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Molecular Design and Synthesis of Quinolones Activated by Steric Effect

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Part A

Molecular Design and Synthesis of Quinolones Activated by Steric Effect

Abstract

The thesis deals with studies on molecular design and synthesis of quinolones activated by steric effect between the 1-methyl and 8-substituent groups.

While the 1-methyl-2-quinolone (**MeQone**) framework is not reactive because of aromatic property in the pyridone ring, 1-methyl-3,6,8-trinitro-2-quinolone (**TNQ**) exhibits extremely high reactivity. Indeed, **TNQ** undergoes *cine*-substitution to afford 4-substituted 6,8-dinitro-1-methyl-2-quinolones upon treatment with versatile nucleophiles. Moreover, **TNQ** also undergoes cycloaddition reactions at the 3- and the 4-positions under mild conditions leading to polycyclic compounds, which reveals that the pyridone moiety of **TNQ** shows nitroalkene property rather than aromatic property. It is considered that the high reactivity of **TNQ** is caused by steric repulsion between the 1-methyl and the 8-nitro groups. In other words, the **MeQone** framework can be sterically activated even in the absence of electronic activation. In the present work, the molecular design and synthesis of the sterically activated **MeQones** was studied on the basis of this hypothesis.

Firstly, reactivity of several kinds of **MeQones** having both 1-methyl and the 8-substituent was predicted by DFT calculation, by which the dihedral angles between N_1 -Me and C_8-R^8 bonds are estimated. The calculated results suggested 1,6-dimethyl-3,8-dinitro-2-quinolone and 1,8-dimethyl-3,6-dinitro-2-quinolone are considered to surely reveal high reactivity as well as **TNQ**. As a result of study on the preparation, the latter quinolone was successfully synthesized in addition to 3,5,7-trinitrated and 3,5-dinitrated 1,8-dimethyl-2-quinolones.

When nitrated 1,8-methyl-2quinolones were subjected to the reactions with

2,4-pentanedione in the presence of triethylamine, the *peri*-substituent (R^5) was found to prevent the *cine*-substitution. Thus, a small nucleophile, potassium cyanide, was employed for estimation of the reactivity of the **MeQone** framework. The high reactivity was maintained, even when the 6-nitro or 8-nitro groups of **TNQ** was replaced with a methyl group, to afford corresponding *cine*-substituted products upon treatment with potassium cyanide. These results strongly support our consideration that the steric repulsion between 1-methyl and 8-methyl groups activated the **MeQone** by disturbing the coplanarity, which decreases aromaticity of the pyridone moiety.

This work affords researchers valuable information for the functionalization of the **MeQone** framework, which is helpful for finding new biologically active compounds.

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Chapter 1 General Introduction

1.1 *Rutaceae* Family of Plants

A *Rutaceae* family, commonly known as the *rue* or *citrus* family, is one of the important worldwide families of plants. This family consist of approximately 160 genera from which many economically valuable chemical compositions are obtained, such as, limonoids, flavonoids, alkaloids, coumarins, and volatile oils.¹ Among these natural products, many kinds of alkaloids have been also isolated, which contain aromatic azaheterocyclic frameworks such as: quinazoline, quinoline, and acridine as the fundamental framework. The major part of quinoline alkaloids are quinolone derivatives, which are classified into four groups: 2-quinolone, 4-quinolone, 1-methyl-2-quinolone and 1-methyl-4-quinolone frameworks (Figure 1.1.1).² All quinolone derivatives exhibit pharmaceutical importance, among which the 1-methyl-2-quinolone (abbreviated as **MeQone** hereafter) derivatives are focused in the present thesis.

More than 300 quinolone alkaloids bearing the **MeQone** framework have been isolated.³ Such naturally occurring **MeQone** derivatives have attracted many researchers' interest, and their isolations, structural determinations, total syntheses, and modifications have been important subjects over the past decades. On the other hand, unnatural **MeQone** derivatives have also attracted much attention recently because of their latent pharmacological and physiological activities. Indeed, various medicinal properties of **MeQone** derivatives have been reported, such as cytotoxic activity,⁴ SRS-A antagonist,⁵ nicotinic agonist,⁶ antitumor activity,⁷ antianemia activity,⁸

antikinestoplastid activity,⁹ antimicrobial activity,¹⁰ antibacterial activity,¹¹ chymase inhibition,¹² and dipeptidyl peptidase IV inhibition¹³ (Figure 1.1.2).

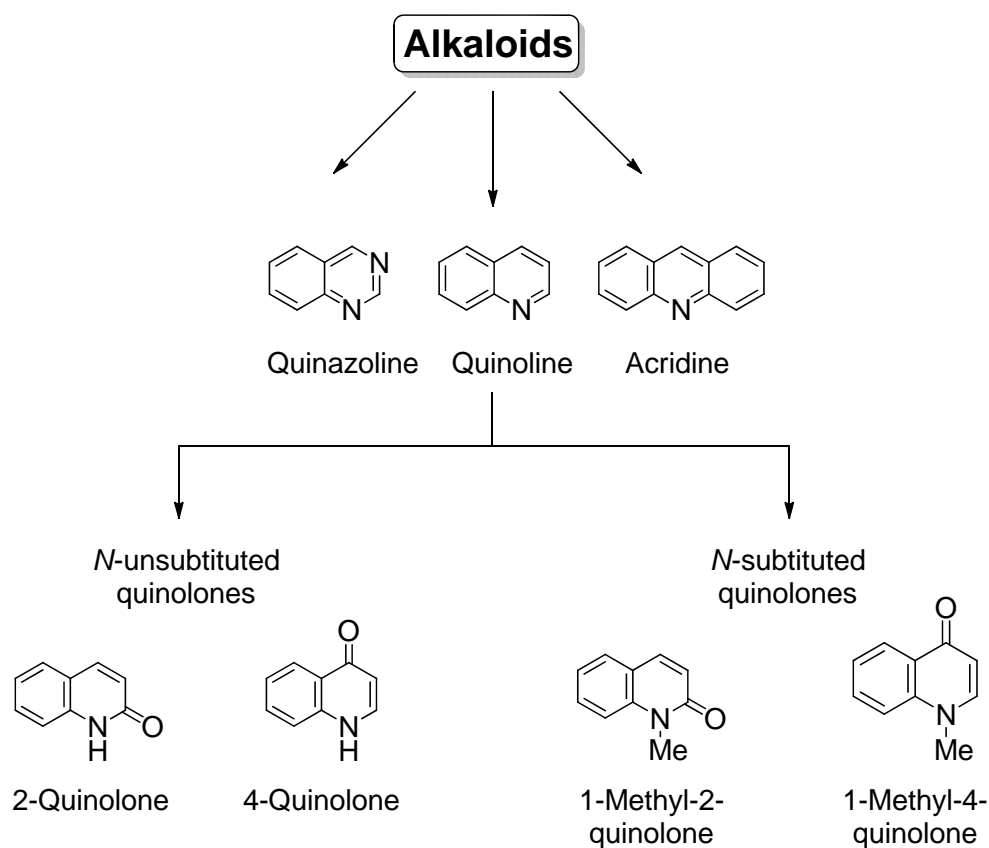
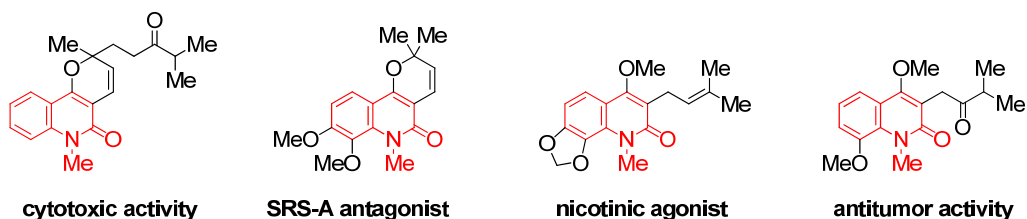


Figure 1.1.1 Alkaloids framework by types of chemical structure

Naturally occurring MeQone derivatives



Unnatural MeQone derivatives

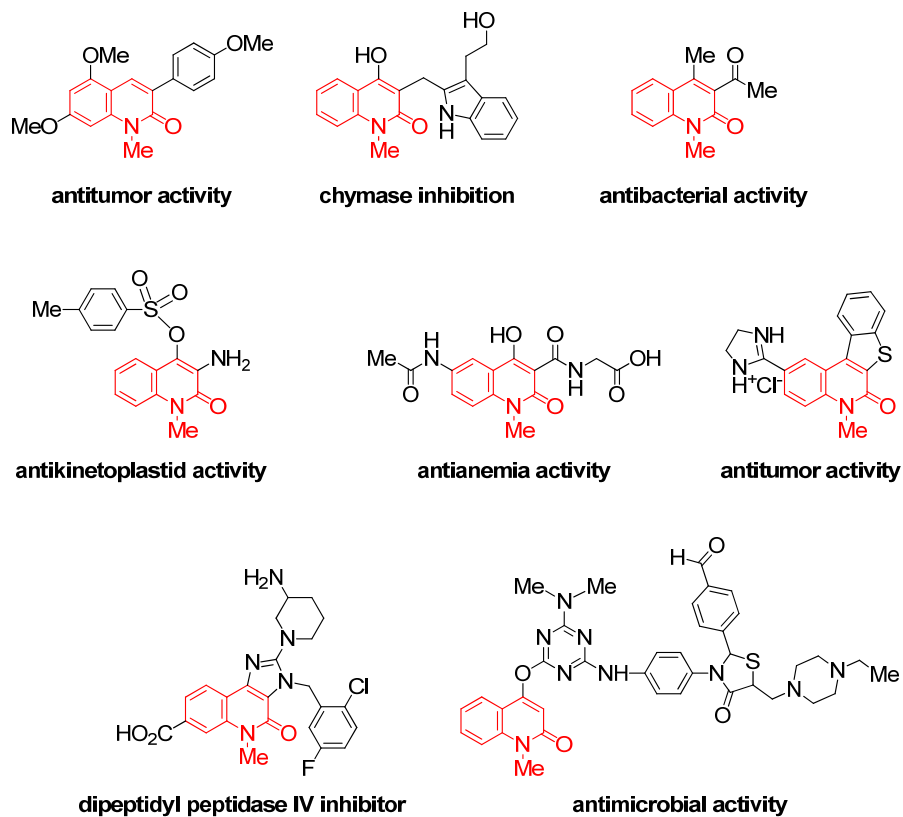


Figure 1.1.2 Examples for naturally occurring and unnatural **MeQone** derivatives

Usually, *N*-unsubstituted 2-quinolone framework is composed of a pyridone moiety and a fused benzene moiety, which exhibits high aromaticity because of the tautomeric quinolinol structure.¹⁴⁻¹⁷ On the other hand, *N*-substituted quinolone (**MeQone**) cannot

have a tautomeric structure; however, the **MeQone** also shows slight aromaticity, which is due to the contribution of the betaine resonance structure (Figure 1.1.3).

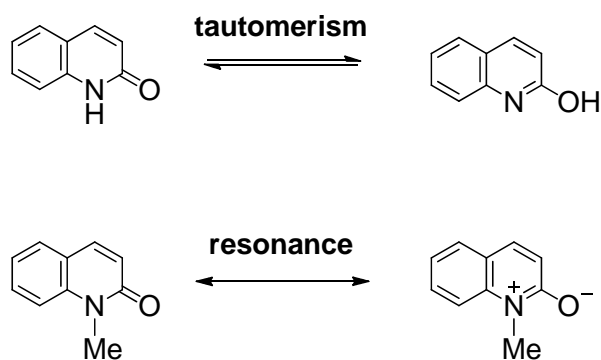


Figure 1.1.3 Structure characteristics of *N*-unsubstituted and substituted 2-quinolones

The aromaticity of the **MeQone** lowers the reactivity, which prevents the direct nucleophilic and electrophilic functionalization. For this reason, it is necessary to develop simple synthesizing and functionalizing methods for construction of **MeQone** derivatives libraries. From this viewpoint, the chemistry of **MeQone** is one of the highly attractive areas even now in spite of vast studies in the past decades.

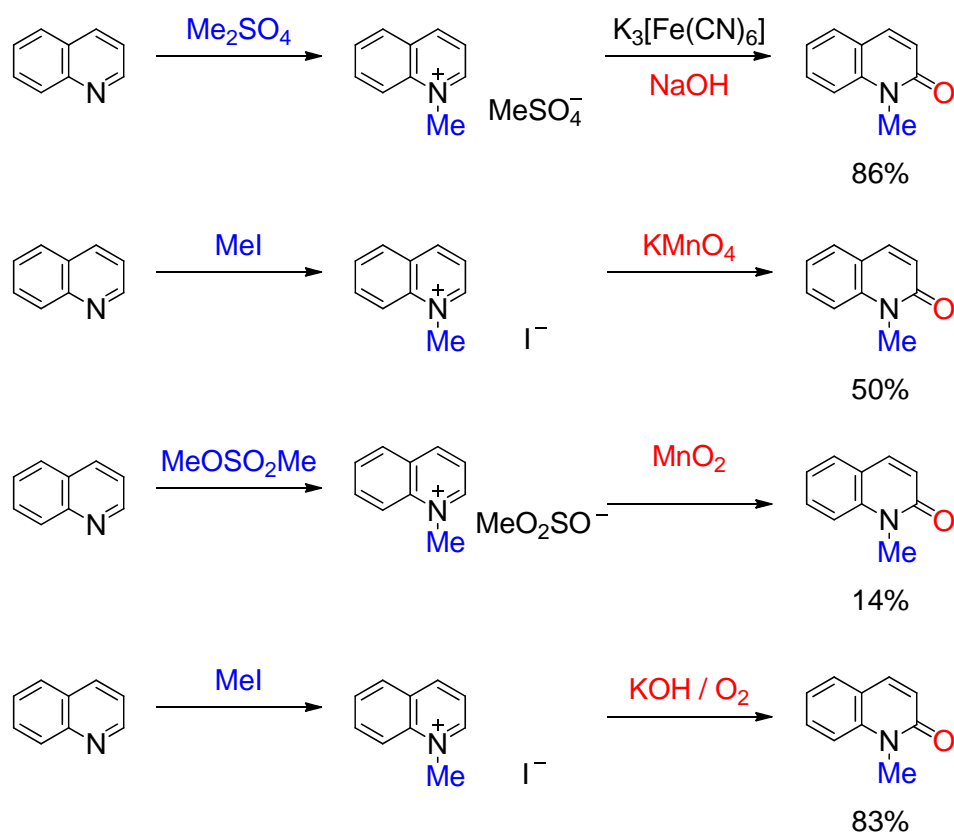
1.2 Synthesis of 1-Methyl-2-quinolones

Construction of the 1-methyl-2-quinolone (**MeQone**) framework is usually performed using three strategies: (1) direct modification of quinoline, (2) construction of a pyridone moiety on the benzene scaffold, and (3) ring transformations, which are supplementary to each other.

1.2.1 Direct modification of quinoline

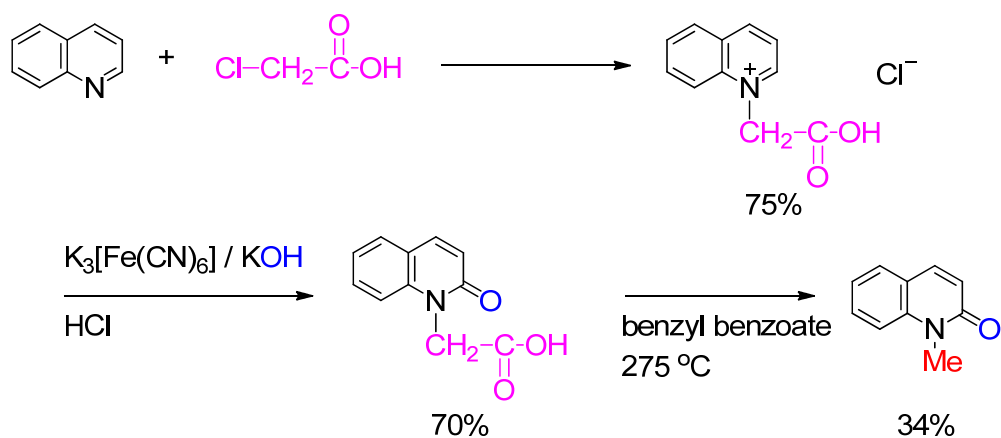
The most available method for the direct modification to **MeQone** is methylation of quinoline, followed by oxidation. Several examples are shown in Scheme 1.2.1.¹⁸⁻²¹ *N*-Methylquinolinium salts are prepared by methylation of quinoline with dimethyl sulfate. In this step, dimethyl sulfite or iodomethane is also usable as the methylating agent. The following oxidation is performed in one-pot using potassium ferricyanide under alkaline conditions. Although oxidation with potassium permanganate or activated manganese dioxide is also possible, the yield of **MeQone** is low. On the other hand, oxidation by molecular oxygen under alkaline conditions is effective to afford **MeQone** in a high yield.

Another approach to **MeQone** is also reported, in which quinoline having a carboxymethyl group is prepared similarly from quinoline and chloroacetic acid. The formed *N*-carboxymethyl-2-quinolone is decarboxylated to afford **MeQone** upon heating in benzyl benzoate at 275 °C, however, this method is not practically used because of severe reaction conditions (Scheme 1.2.2).²²

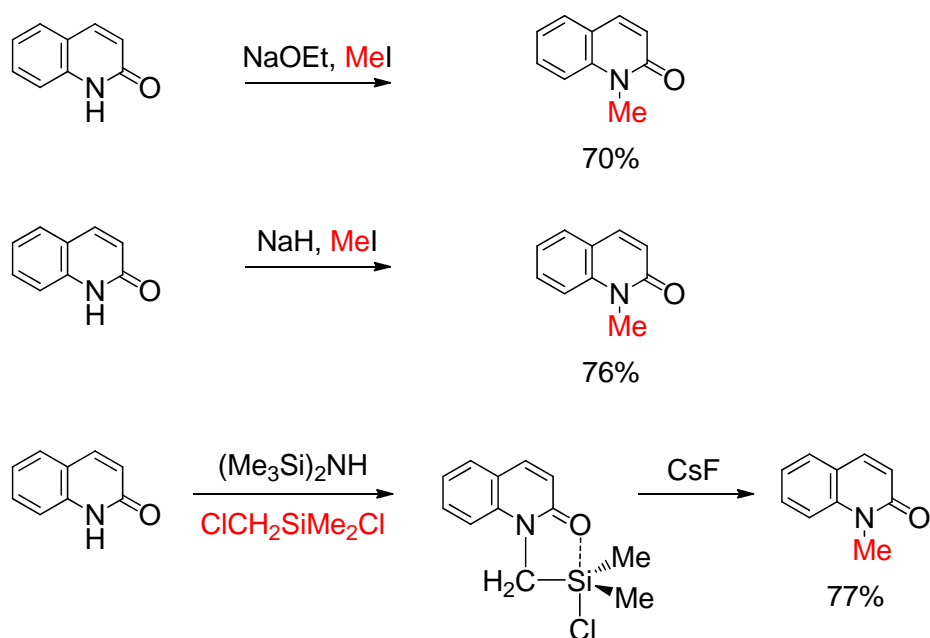


Scheme 1.2.1 Preparation of **MeQone** from quinoline

Alternative procedure for synthesizing **MeQone** is methylation of 2-quinolone which is well known as carbostyryl and commercially available (Scheme 1.2.3). Since 2-quinolone has a 2-hydroxyquinoline, its anion shows ambident nucleophilicity. In spite of this worry, *N*-methylation of 2-quinolone proceeds to afford **MeQone** in over 70% yield when 2-quinolone is allowed to react with methyl iodide,²³ using sodium ethoxide or sodium hydride as a base.²⁴ Recently, a chemoselective methylation of 2-quinolone using with chloromethyl(dimethyl)silyl chloride and hexamethyldisilazane is also documented.²⁵



Scheme 1.2.2 Decarboxylation of *N*-carboxymethyl-2-quinolone



Scheme 1.2.3 Methylation of 2-quinolone

1.2.2 Construction of a pyridone moiety on the benzene scaffold

For unsubstituted **MeQone** framework, direct modification method is useful. However, when substituted **MeQone** is necessary, direct modification method is not usable, construction of a pyridone ring on the benzene scaffold is also developed, including: (A) formation of C₄-C_{4a} bond; (B) formation of C₃-C₄ bond; (C) formation of N₁-C₂ and C₄-C_{4a} bonds; and (D) formation of N₁-C₂ and C₃-C₄ bonds (Figure 1.2.1).

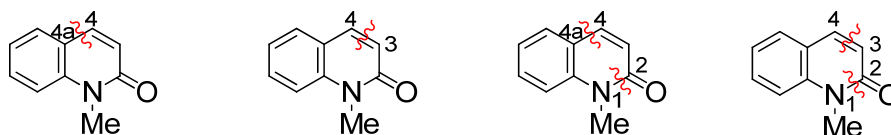


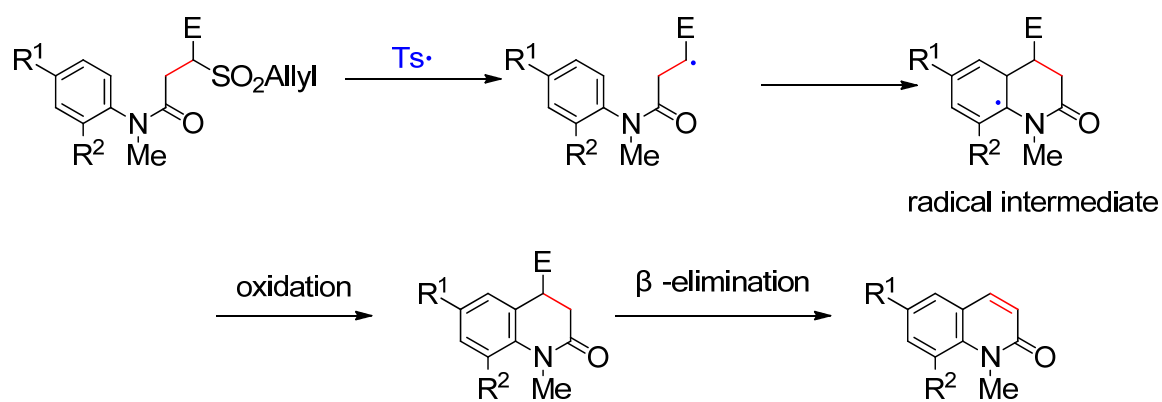
Figure 1.2.1 Construction of a pyridone moiety on the benzene scaffold

A. Formation of C₄-C_{4a} bond

Radical cyclization reactions are often found on the intramolecular cyclization that yield cyclic products, when aniline derivatives possessing properly designed amino group are available, intramolecular radical cyclization proceeds to afford quinolone derivatives.

Substituted **MeQones** could be prepared by free radical cyclization of alkylsulfonyl and alkylthio substituted aromatic amide derivatives, in which carbon radicals can be generated efficiently from the sulfonyl radical induced reaction of allylsulfones or the oxidation of benzene ring with manganese(III) acetate, and undergo 6-membered ring cyclization onto the aromatic ring effectively to provide quinolones (Table 1.2.1).²⁶

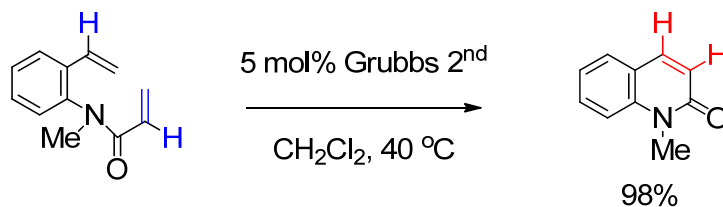
Table 1.2.1 Radical cyclization reaction for substituted **MeQones**



Substrate			Yield/%
E	R ¹	R ²	
AllylSO ₂	Me	H	67
AllylSO ₂	H	H	61
AllylSO ₂	H	Me	63
AllylSO ₂	Cl	H	57
AllylSO ₂	CO ₂ Me	H	55
Ms	Me	H	73
Ms	Cl	H	64

B. Formation of C₃-C₄ bond

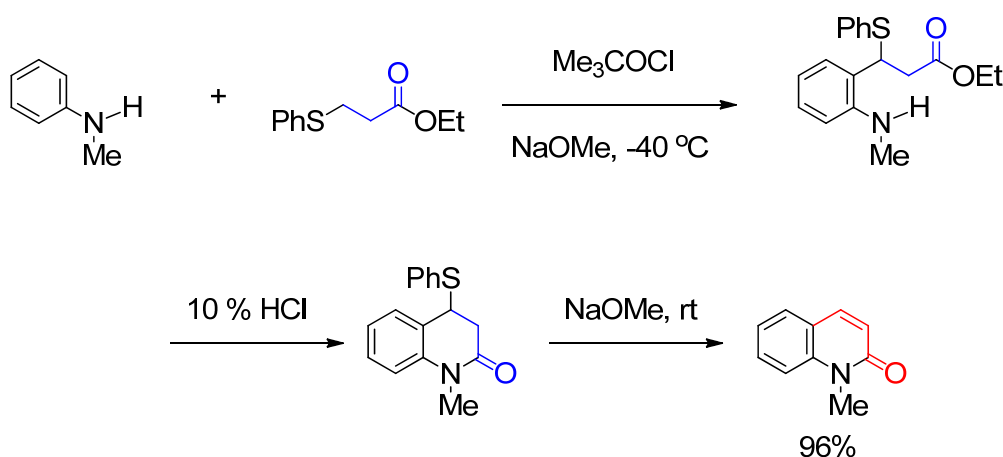
Ring closing metathesis entails the redistribution of fragments of alkenes by the cleavage and regeneration of carbon-carbon double bonds, and has become the method of choice for the formation of cyclic targets including heterocycles. For instance, ring closing metathesis of *N*-phenylacrylamide is a good choice for the synthesis of quinolones. A variety of analogs are prepared varying the substituents around the *N*-phenylacrylamide core in order to explore the effects of the substituents on the reaction efficiency. The reaction is general in scope providing good to excellent yields of the corresponding quinolones. Substitution at nitrogen with a methyl group is well tolerated and provides excellent yields of the corresponding **MeQone** framework (Scheme 1.2.4).²⁷



Scheme 1.2.4 Ring closing metathesis of substituted *N*-phenylacrylamide

C. Formation of N₁-C₂ and C₄-C_{4a} bonds

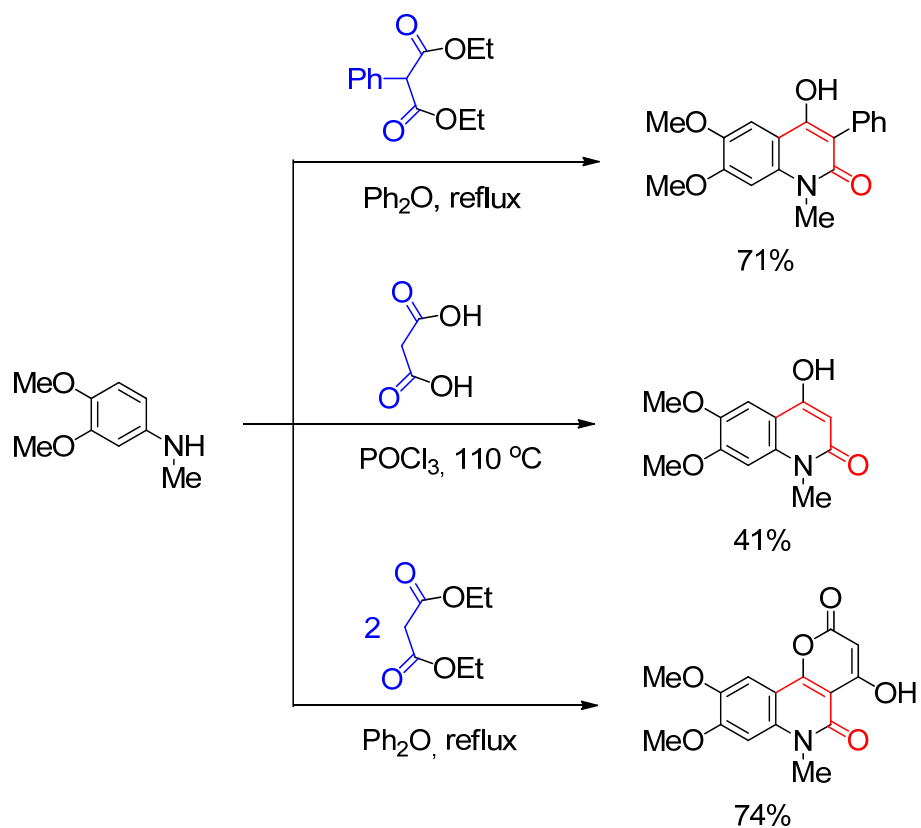
The [2,3] sigmatropic rearrangement of ylides derived from *N*-arylazasulphonium salts has proved to be an extremely useful reaction for the exclusive *ortho*-substitution of aromatic amines. Conversion of aniline into **MeQone** via [2,3] sigmatropic rearrangement is available, which involves the sequential reaction of *N*-methylaniline with *t*-butyl hypochlorite, ethyl 3-phenylthiopropionate, and sodium methoxide to produce the reactive intermediate (2-ethoxycarbonyl-1-phenylthioethyl)-*N*-methyl-aniline, which is readily converted into the aforementioned product. (Scheme 1.2.5).²⁸



Scheme 1.2.5 Conversion of aniline into **MeQone**

Moreover, 2-substituted malonic acid derivatives are known to be very useful reagents in the field of organic synthesis. Besides the preparation of simple derivatives such as malonates or malonamides, malonic acid derivatives react by cyclocondensation with dinucleophiles to afford 5-, 6- and 7-membered rings, and give a variety of so-called “malonyl heterocycles” which possess as structural element a 1,3-dicarbonyl moiety or its enolized tautomeric 1-oxo-3-hydroxy form.²⁹ When appropriately

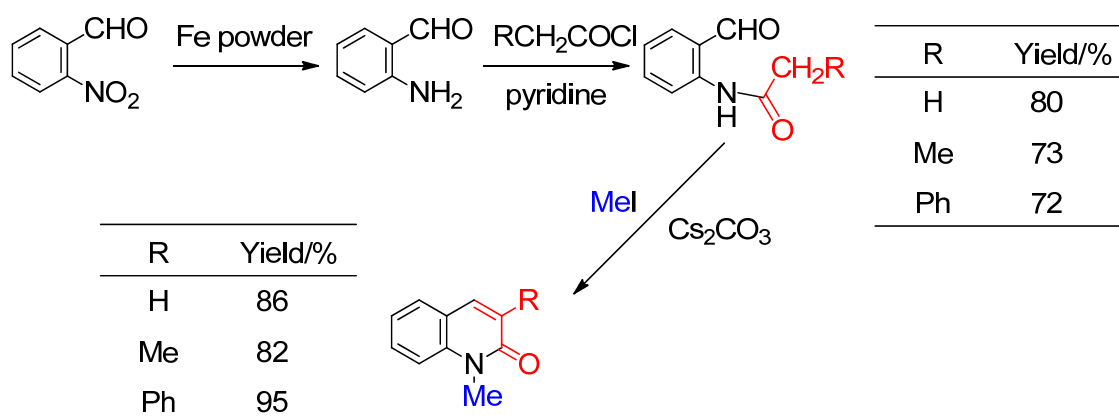
substituted aniline react with alkyl- or aryl-substituted malonates, malonic acid, or diethylmalonate, the corresponding 4-hydroxycarbostyrils and pyranoquinolones could also be prepared (Scheme 1.2.6).³⁰



Scheme 1.2.6 Synthesis of **MeQones** from aniline with malonic acid derivatives

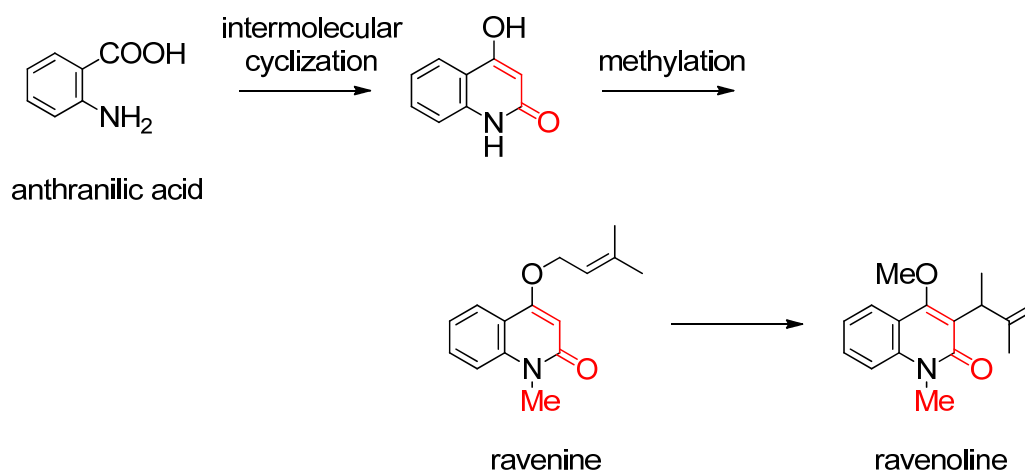
D. Formation of N₁-C₂ and C₃-C₄ bonds

2-Aminobenzaldehyde and its derivatives are key intermediates in heterocyclic synthesis. Thus the Friedländer synthesis of quinolones (base-catalyzed condensation of 2-aminobenzaldehyde with aliphatic aldehydes and ketones) is widely used. Most syntheses of 2-aminobenzaldehydes involve more than one step and at best are moderate in yield. The synthesis of 2-aminobenzaldehyde itself has been reported from easily derived precursors such as 2-nitroaniline. For example, 2-nitrobenzaldehydes could be reduced with iron powder to 2-aminobenzaldehydes, which react immediately with acyl chlorides to provide 2-carboxamidobenzaldehydes. The alkylation reaction of the preformed 2-quinolone ring with alkyl halide gives a mixture of *N*- and *O*-alkylated products. Thus, to prepare 1,3-disubstituted 2-quinolones from 2-carboxamidobenzaldehydes, *N*-alkylation of 2-carboxamidobenzaldehydes and subsequent cyclization of the resulting *N*-alkyl-2-carboxamidobenzaldehyde would be a desirable choice to afford 3-substituted **MeQones** (Scheme 1.2.7).³¹



Scheme 1.2.7 Cyclization of amide to 3-substituted **MeQones**

Moreover, several quinoline alkaloids derived from anthranilic acid have also been reported. In this biosynthetic sequence, 4-hydroxy-2-quinolone is prepared first from 2-aminobenzoic acid, and then methylation and other chemical conversion to furnish **MeQone** derivatives (Scheme 1.2.8).^{3b}

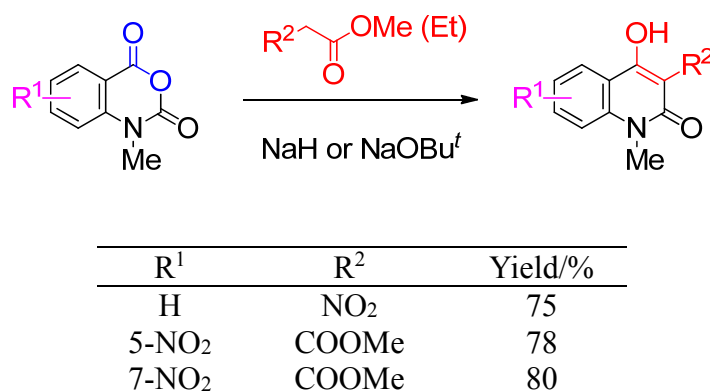


Scheme 1.2.8 Preparation of **MeQone** derivatives from anthranilic acid

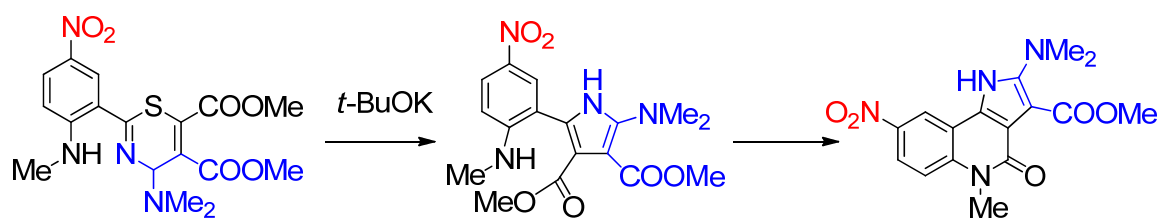
1.2.3 Ring transformation to 1-methyl-2-quinolones

Ring transformation is also a useful procedure for construction of functionalized heterocyclic compounds which are not easily prepared by alternative methods. Substrates for such reactions are required to have a good leaving group as a partial structure. From the viewpoint of constructing the **MeQone** framework, isatoic anhydride is the most suitable substrate (Table 1.2.2). **MeQones** having a nitro group on the benzene ring are available by the ring transformation of nitrated isatoic anhydrides with dimethyl malonate accompanying decarboxylation.^{32,33} The use of ethyl nitroacetate instead of dimethyl malonate enables the synthesis of 3-nitro-2-quinolone.^{34,35}

Table 1.2.2 Ring transformation of isatoic anhydride leading to **MeQones**



As another example, 2-(2-aminophenyl)-1,3-thiazine derivatives are also usable as a substrate for the ring transformation, which results in the formation of pyrroloquinoline derivatives. In the present reaction, 2-(2-aminophenyl)pyrrole is formed as an intermediate, and the subsequent intramolecular nucleophilic substitution forms the pyridone moiety (Scheme 1.2.9).³⁶



Scheme 1.2.9 Ring transformation of aminophenyl-1,3-thiazine

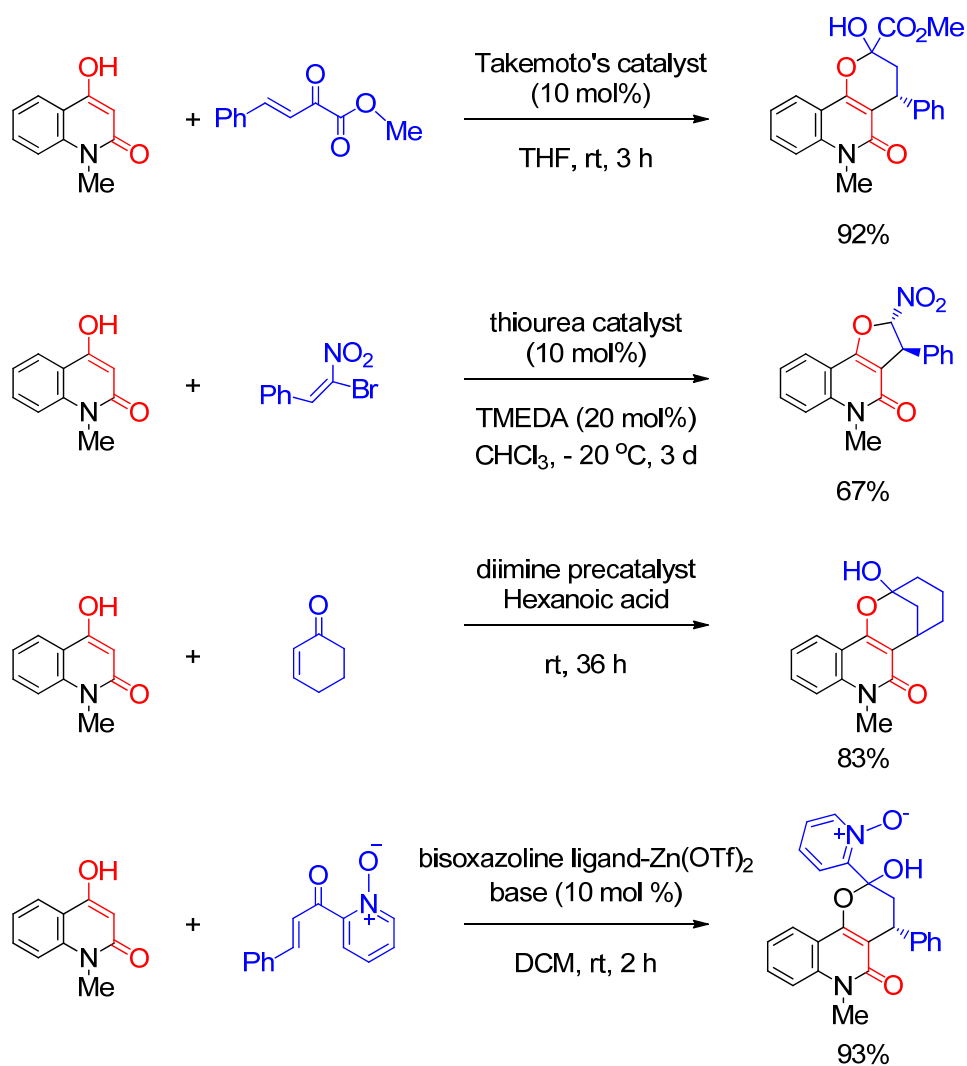
1.3 Functionalization of 1-Methyl-2-quinolones

1.3.1 Cyclization of MeQone-OH⁴

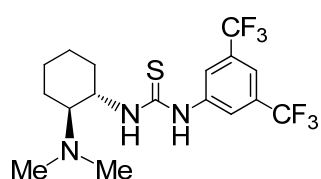
Quinolones constitute an important class of heterocycles that is not only frequently employed as starting materials for the preparation of more complex aromatic ring systems but also a key component of numerous natural biologically active compounds. For instance, **MeQone** with 4-hydroxy group (abbreviated as **MeQone-OH⁴**), which is prepared by condensation of *N*-methylaniline and malonic acid, serves as a significant scaffold for 5/6-membered ring construction to afford [*c*]-fused **MeQone** derivatives.

A. Ring construction induced by Michael addition of 4-hydroxy group

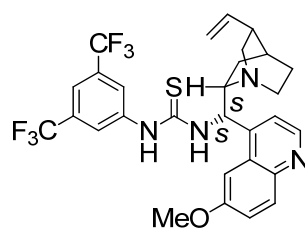
The Michael addition is one of the fundamental C-C bond forming reactions using a conjugated olefin. 1,3-Dicarbonyl compounds (active methylene compounds) are often employed as a good nucleophile in the present reaction. **MeQone-OH⁴** is regarded as an enol form of a cyclic 1,3-dicarbonyl compound, whose 3-position reveals nucleophilicity. When **MeQone-OH⁴** is subjected to the reaction with a conjugated olefin, Michael addition followed by ring closure with a hydroxy group proceeds to furnish pyrano[3,2-*c*]quinolones or furo[3,2-*c*]quinolones. Furthermore, catalytic asymmetric Michael addition is also possible when the reaction is conducted in the presence of a chiral amine as an organocatalyst. Indeed, high enantioselectivities have been obtained. As a Michael acceptor, α,β -unsaturated esters,³⁵ (*E*)- α -bromonitrostyrenes,³⁶ cyclic enones,³⁷ and 2-enoylpyridine *N*-oxides³⁸ have afforded successful results (Scheme 1.3.1).



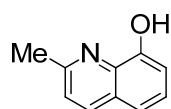
Structure of catalysts:



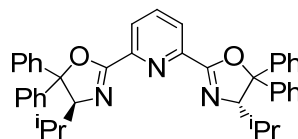
Takemoto's catalyst



thiourea catalyst



diimine precatalyst



bisoxazoline ligand

Scheme 1.3.1 Michael additions of MeQone-OH⁴

B. Multicomponent reactions of MeQone-OH⁴

Multicomponent reactions (MCRs) are efficient and effective methods in the sustainable and diversity-oriented synthesis of heterocycles. MCRs are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product.

1,3-Diketones have been widely employed as the useful components in syntheses of natural products and biologically active compounds through MCRs with aliphatic aldehydes as electrophiles and nucleophilic partners, and give structurally different heterocyclic compounds (Scheme 1.3.2).³⁹⁻⁴²

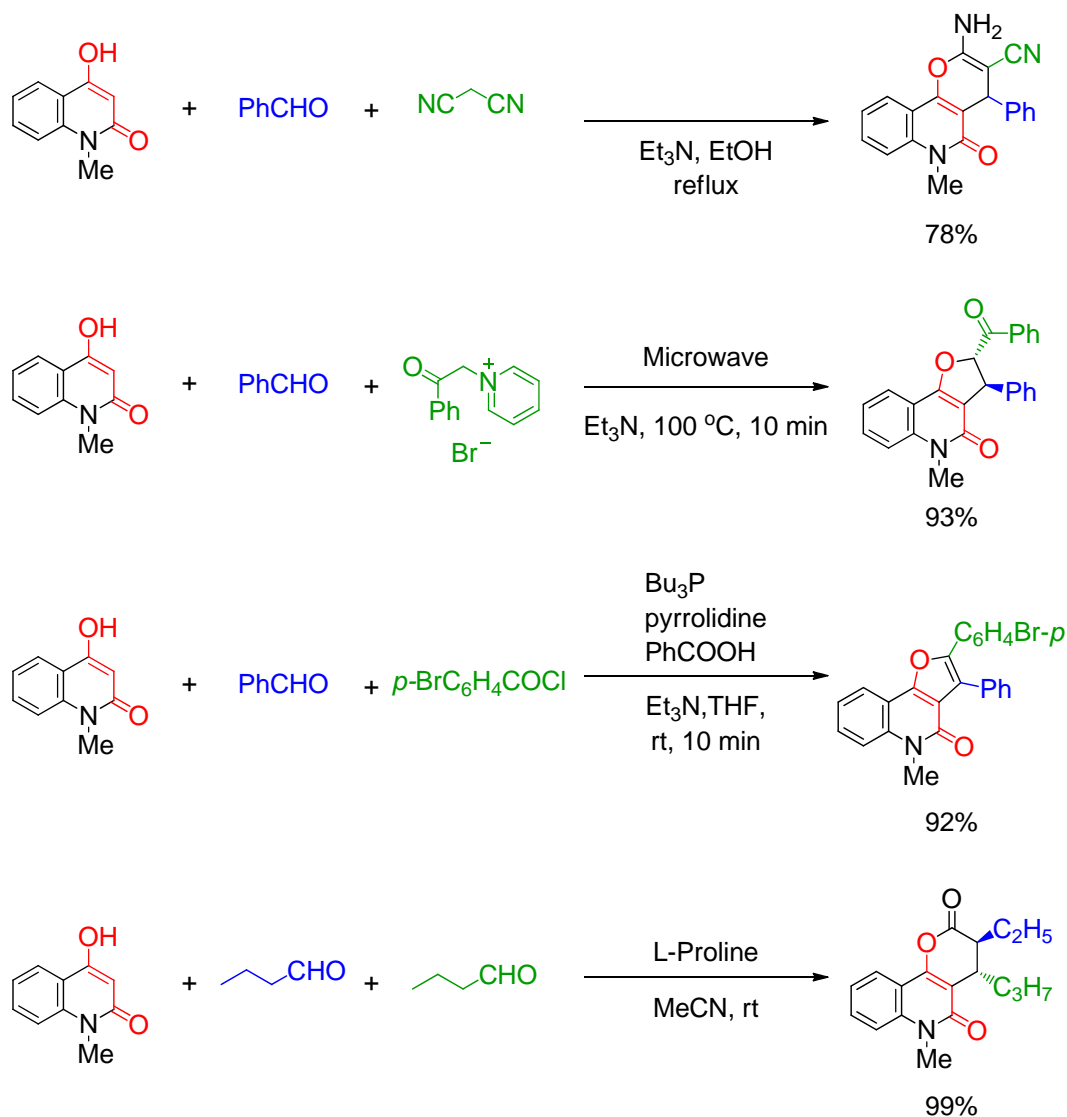
The utilization of MCRs lead to the development of compound libraries based on pyrano[3,2-*c*]quinolone scaffolds, which are commonly found in structurally complex alkaloids manifesting diverse biological activities. A three-component reaction of **MeQone-OH⁴** with malononitrile and various aromatic aldehydes in a 1:1:1 ratio proceeds smoothly in refluxing ethanol containing a small quantity of triethylamine to obtain corresponding analogs.³⁹

Similarly, three-component domino reactions of **MeQone-OH⁴**, aromatic aldehydes and 1-(2-oxo-2-arylethyl)pyridinium bromides in water in the presence of a catalytic amount of triethylamine are studied. It is pertinent to note that domino MCRs are very useful for the syntheses of molecules of structural diversity and complexity from readily available simple starting materials.⁴⁰

Zwitterions with phosphine moieties attract much attention of scientists because of not only the special interest in their specific structures and properties but also their potential application in organic synthesis. Highly functional phosphorus zwitterions via

three component reactions of **MeQone-OH⁴**, aldehydes and tributylphosphine can be applied successfully in the reaction with a wide variety of acid chlorides to afford highly functionalized **MeQone** derivatives in good to excellent yields.⁴¹

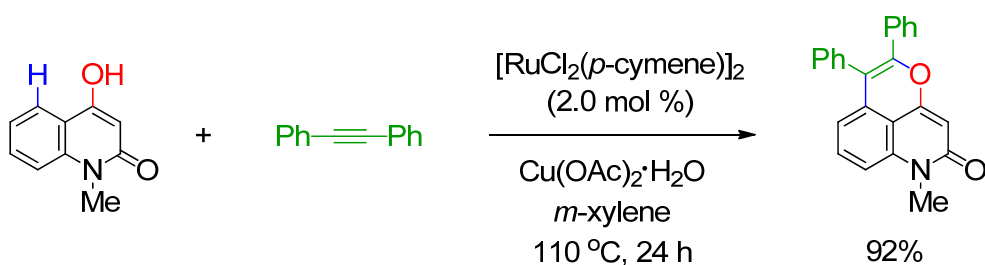
Furthermore, a highly efficient route for the synthesis of valuable 3,4-substituted chromenone derivatives by the reaction of 1,3-diketones with aldehydes in the presence of L-proline is developed. These reactions take advantage of readily available starting materials and follow a Knoevenagel condensation/Michael addition/hemiacetalization domino process.⁴²



Scheme 1.3.2 Multi component reactions of **MeQone-OH⁴**

C. C-H/O-H bond functionalization of MeQone-OH⁴

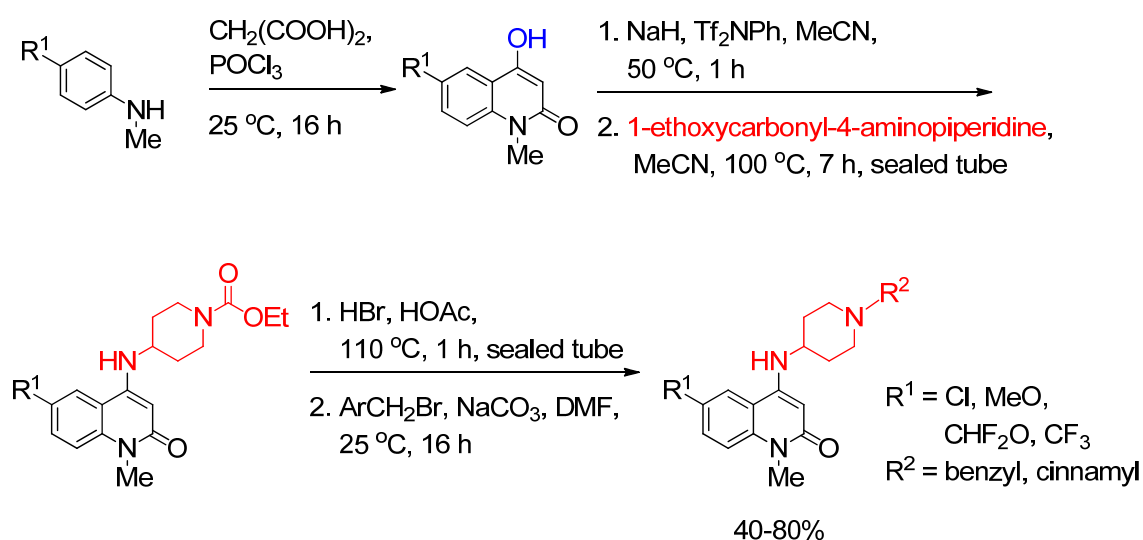
Oxidative C-H bond functionalization provides step-economical access to important bioactive heteroarenes, ruthenium-catalyzed oxidative C-H bond functionalization through hydroxy assistance has been reported. A ruthenium(II) catalyst allow the efficient annulation of alkynes by **MeQone-OH⁴** to yield fluorescent annulated pyrans and give step-economical access to diversely decorated coumarins and quinolin-2-ones with ample scope. (Scheme 1.3.3).⁴³



Scheme 1.3.3 Ruthenium-catalyzed annulation of **MeQone-OH⁴**

1.3.2 Substitution of MeQone-OH⁴

A hydroxy group at the 4-position of **MeQone-OH⁴** also serves as a leaving group via triflate **MeQone-OTf⁴**, by which other functional groups can be introduced into the **MeQone** framework. When **MeQone-OTf⁴** is treated with protected 4-aminopiperidine, substitution proceeds to afford 4-aminated **MeQone** derivatives, that showing high bioactivity as potent, functionally active melanin concentrating hormone antagonists.⁴⁴ Deprotection followed by reaction with the appropriate benzyl or cinnamyl halide affords corresponding 4-functionalized **MeQone** derivatives (Scheme 1.3.4).

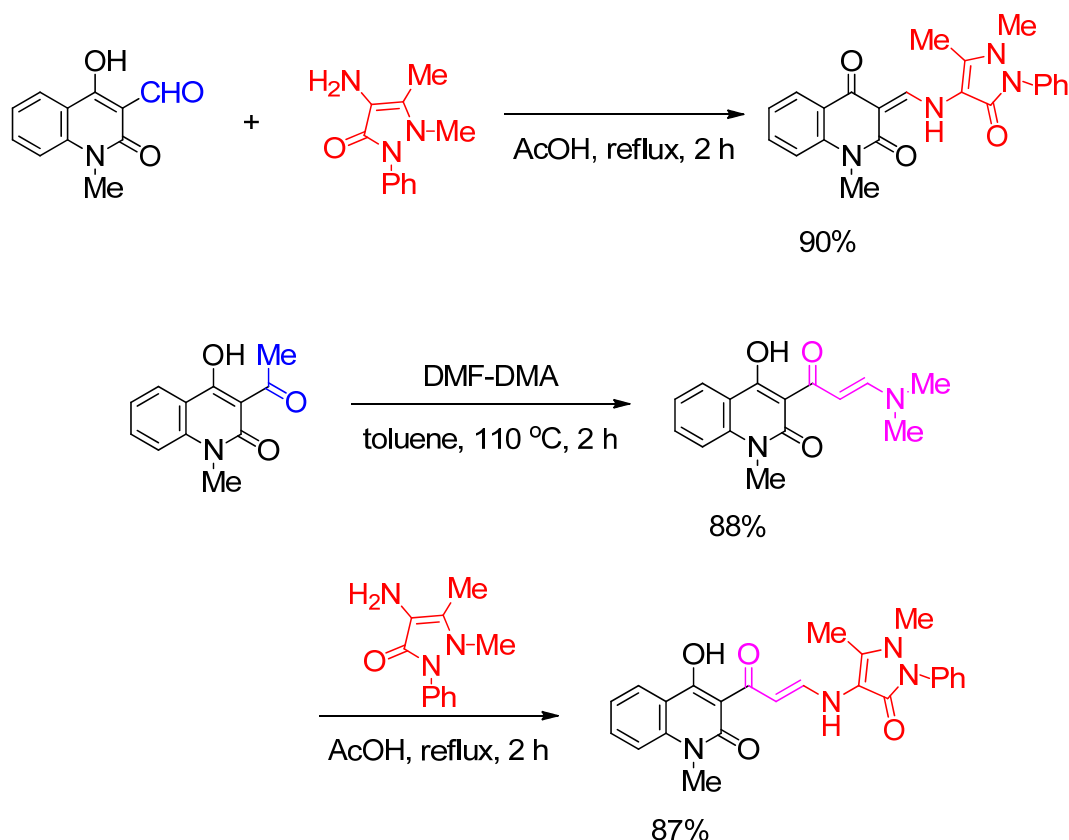


Scheme 1.3.4 Substitution of **MeQones-OH⁴**

1.3.3 Condensation of MeQone-CHO³/ MeQone-Ac³

A carbonyl group is a reactive functional group to reveal diverse reactivity, and leads to versatile functional groups. When **MeQone-CHO³** is treated with 4-aminopyrazol-2-one, condensation proceeds to afford an enamine. Since **MeQone-OH⁴** is a kind of 1,3-dicarbonyl compound, the enamine moiety is incorporated into a conjugated system with two carbonyl groups.

An acetyl group also serves as a scaffold for functionalization of the **MeQone** framework. Condensation of an acetyl group with dimethylformamide affords unsaturated amide, which can undergo the further functionalization (Scheme 1.3.5).⁴⁵

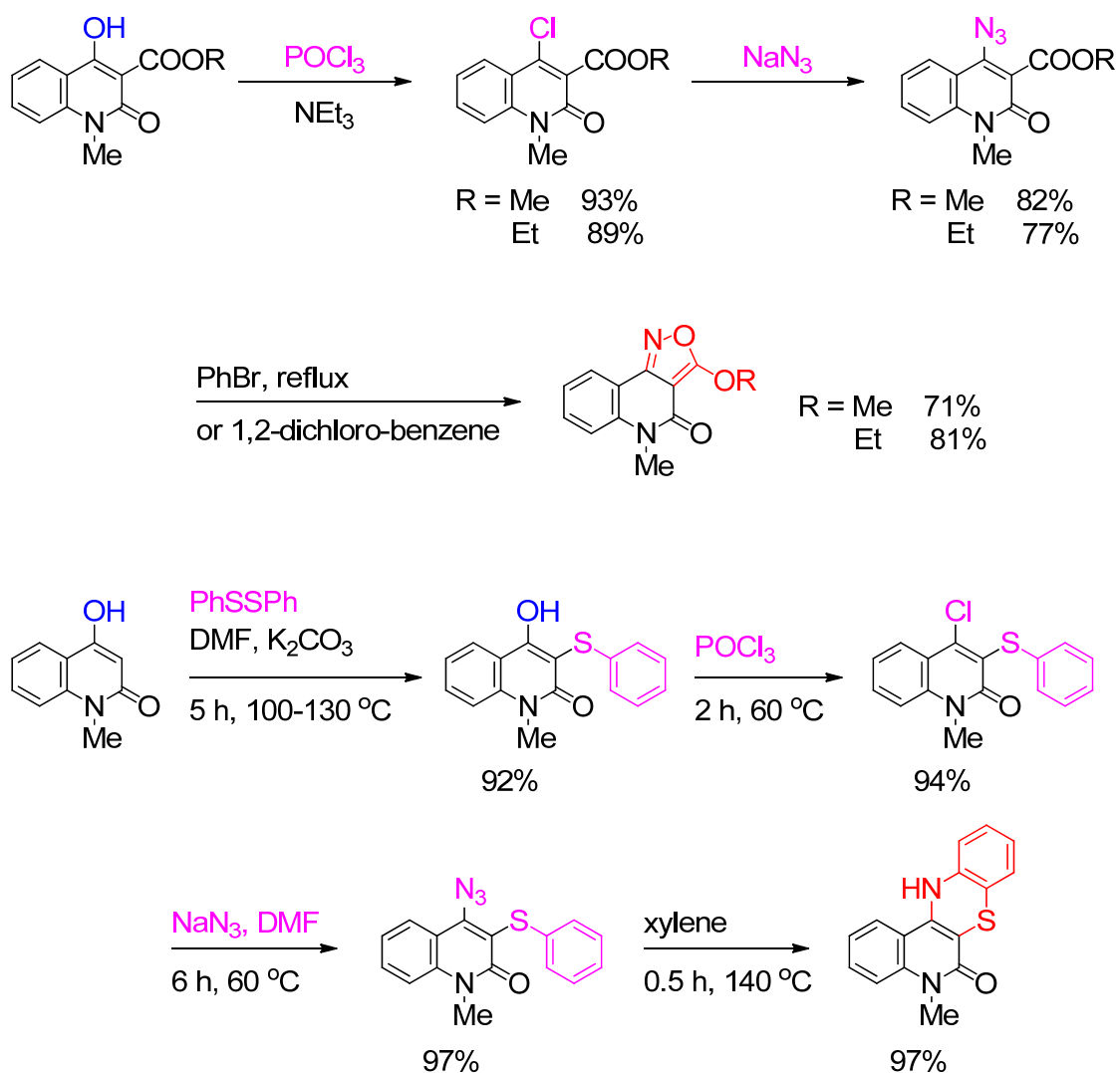


Scheme 1.3.5 Condensation of MeQone-CHO³/ MeQone-Ac³

1.3.4 Conversion of **MeQone-OH⁴** to **MeQone-N₃⁴** via **MeQone-Cl⁴** and cyclization of **MeQone-N₃⁴**

MeQone-OH⁴ is also converted to **MeQone-Cl⁴** upon treatment with phosphorous oxychloride, which is then transformed to **MeQone-N₃⁴** by nucleophilic substitution with sodium azide. Vicinally functionalized aromatic azides are known to decompose on thermolysis or photolysis followed by a cyclization leading to heterocycles, either via a nitrene or an electrocyclic mechanism. Mainly, this type of cyclization leads to five-membered heterocycles. When **MeQone-N₃⁴** having an ester function at the 3-position is heated, thermolysis occurs with loss of nitrogen gas, and the resultant nitrene reacts with the vicinal carbonyl group to form a [c]-fused isoxazole ring.⁴⁶

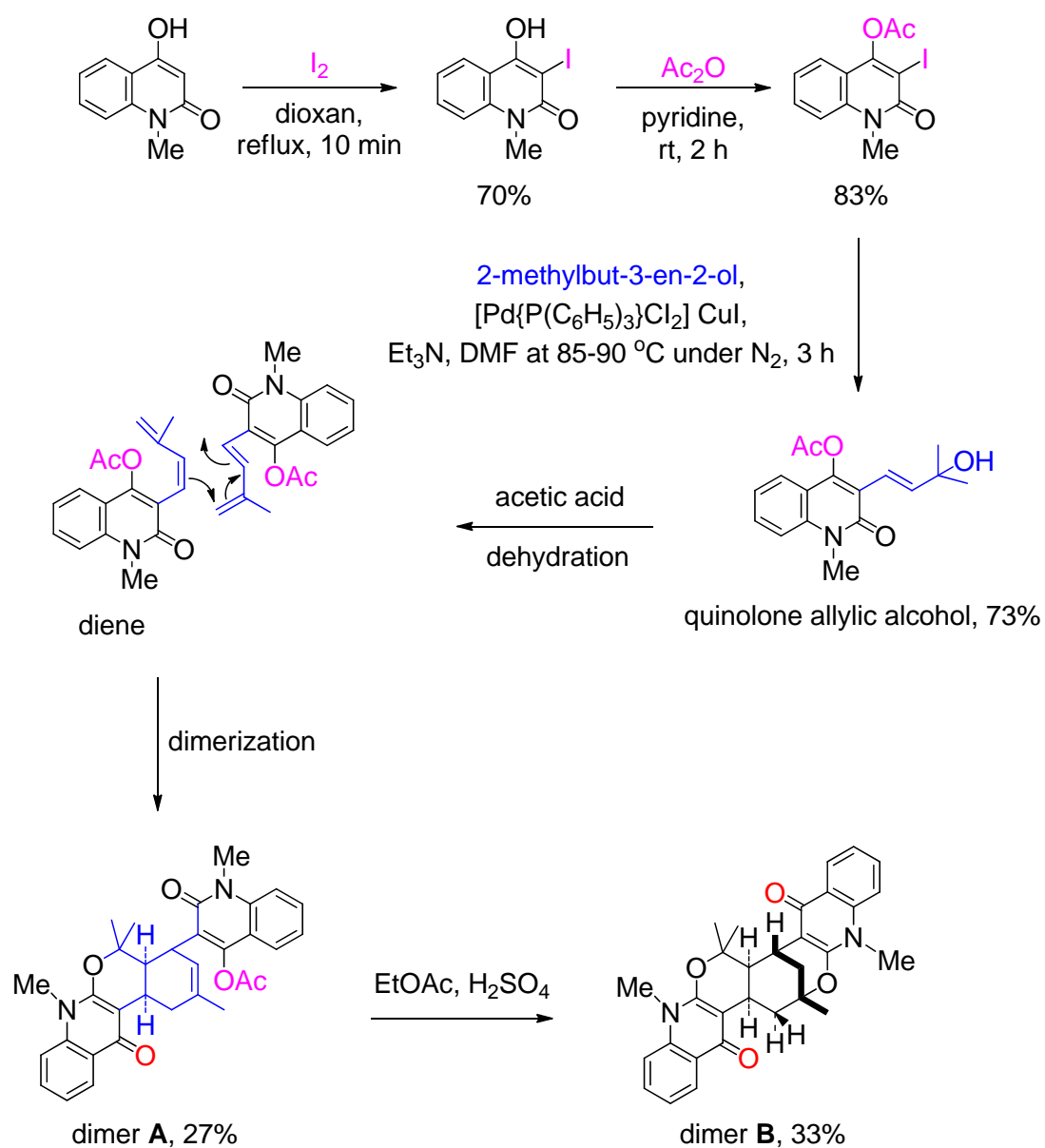
On the other hand, formation of six-membered thiazine ring is also observed when a phenylthio group is substituted at the 3-position of **MeQone-N₃⁴**, in which the intermediately formed nitrene undergoes the electrophilic substitution with a phenyl group giving quinolino[3,4-*b*][1,4]benzothiazine (Scheme 1.3.6).⁴⁷



Scheme 1.3.6 Cyclization of **MeQone- N_3** ⁴

1.3.5 Dimerization of MeQone-OAc⁴

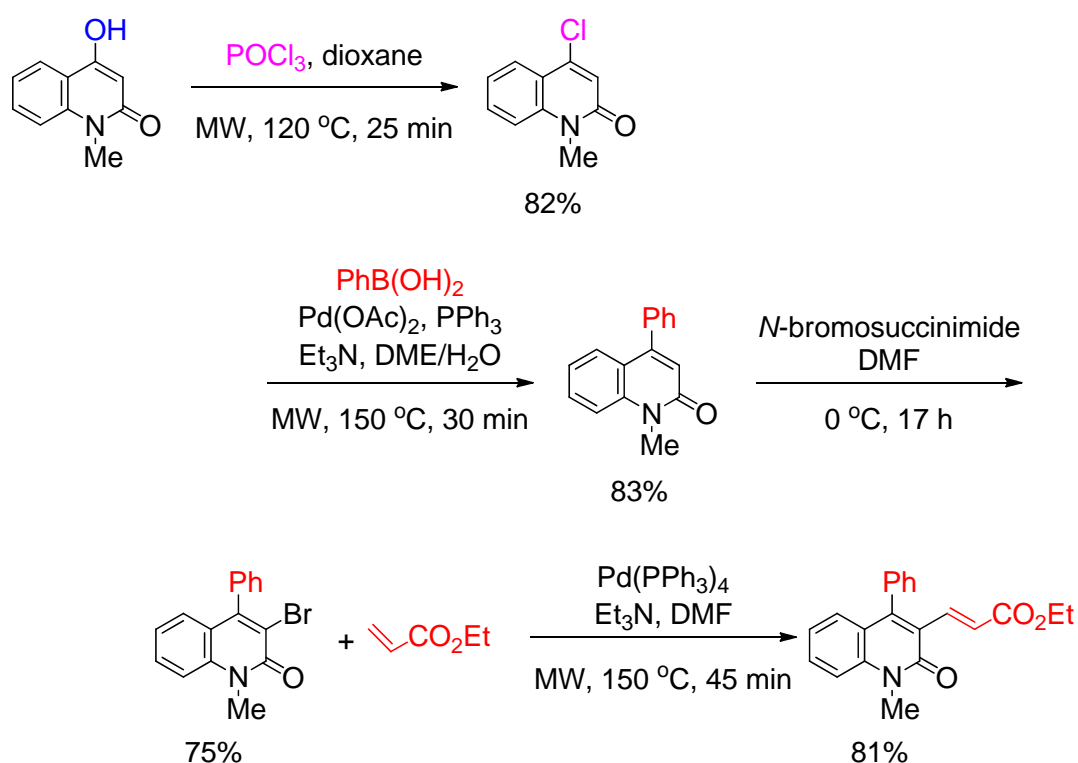
The biosynthesis of dimeric quinolone alkaloids has also been discussed, which starts from **MeQone-OH⁴** (Scheme 1.3.7). Nucleophilic substitution of iodine with **MeQone-OH⁴** results in the 3-iodo-4-hydroxyquinolone derivative. After the protection of a hydroxy group as an acetoxy group, the compound is subjected to the Heck reaction with an allylic alcohol followed by acid-catalyzed dehydration to afford diene-substituted quinolone. The resultant dienes undergo the dimerization by Diels-Alder cycloaddition, and a pyran ring is concomitantly formed accompanied by deacetylation leading to tetracyclic dimer **A** and heptacyclic dimer **B** having a similar type structure of the dimeric quinolone alkaloids, paraensidimerins.⁴⁸



Scheme 1.3.7 Dimerization of MeQone-OAc⁴

1.3.6 Suzuki and Heck reactions of MeQone-Cl⁴

MeQone-Cl⁴ also serves as a substrate for C-C bond forming coupling reactions such as the Suzuki and the Heck reactions. When **MeQone-Cl⁴** is allowed to react with phenylboronic acid in the presence of palladium catalyst, the Suzuki coupling proceeds to afford **MeQone-Ph⁴**. The following bromination at the 3-position using *N*-bromosuccinimide is performed for the subsequent Heck vinylation. The palladium-catalyzed Heck reaction of **MeQone-Br³Ph⁴** with acrylate enables to introduce an acrylic ester moiety to the quinolone core (Scheme 1.3.8).⁴⁹



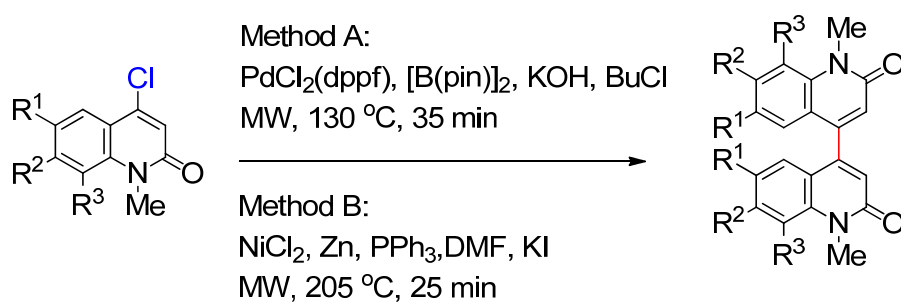
Scheme 1.3.8 Modification of **MeQone** framework using C-C cross coupling reactions

Substituted biaryls are often found in many natural products, pharmaceuticals, herbicides, and fine chemicals.^{50,51} In addition, biaryls are applied as chiral ligands in

catalysis, as liquid crystals or organic conductors.⁵⁰ To the contrary, bisheterocycles often display similarly interesting biological and physical properties.⁵¹⁻⁵⁴

Functionalized 4,4'-bisquinolones can be efficiently synthesized by microwave-assisted palladium(0)-catalyzed one-pot borylation/Suzuki cross-coupling reactions or via nickel(0)-mediated homocouplings of **MeQone-Cl⁴** precursors (Table 1.3.1).⁵⁵

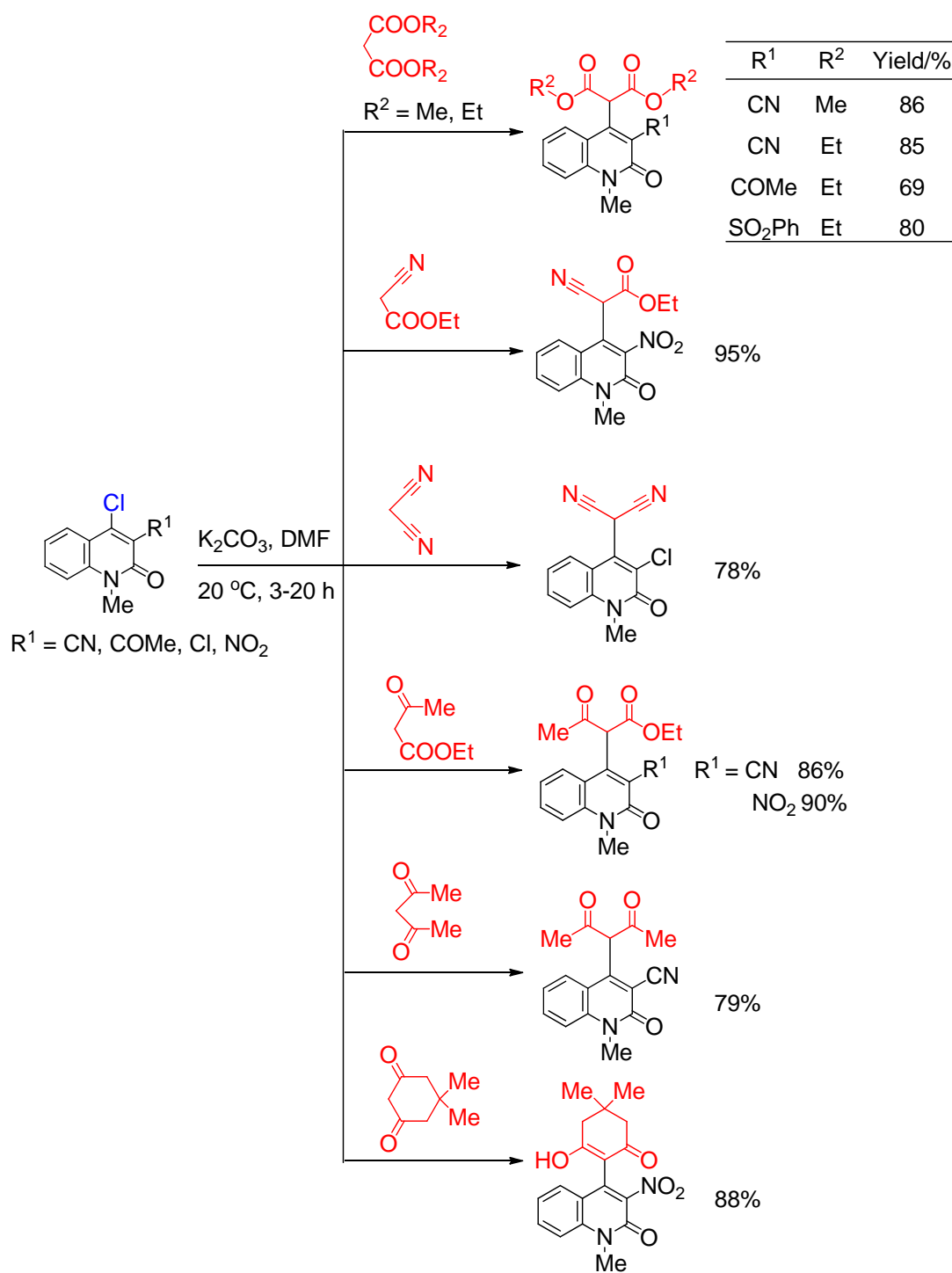
Table 1.3.1 Symmetrical bisquinolones via metal-catalyzed cross-coupling and homocoupling reactions



Substrate			Yield/%	
R ¹	R ²	R ³	Method A	Method B
H	H	H	85	90
OMe	H	H	83	70
H	OMe	H	70	74
OMe	OMe	H	82	41

1.3.7 Substitution of MeQone-Cl⁴

MeQone-Cl⁴ having an electron-withdrawing group at the 3-position serves as a good scaffold for introducing a functionality to the 4-position by nucleophilic substitution of CH-acid such as diesters, β -keto esters, β -diketones, malononitriles, and cyano esters (Scheme 1.3.9).⁵⁶ The resultant **MeQones** attract great interest either due to their biological properties or their use as synthons for further reactions.

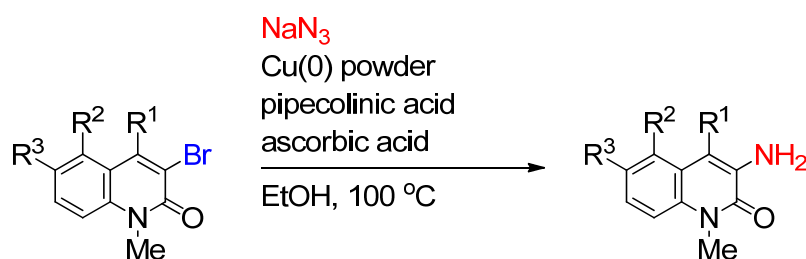


Scheme 1.3.9 Substitution of **MeQone-Cl**

1.3.8 Reduction of MeQone-Br³

3-Substituted-2-quinolones are an important class of heteroaromatic compounds, which have attracted considerable attention because of their pharmacological properties.⁵⁷ One of the most important subfamilies of 2-quinolones is the 3-amino-2quinolone class, whose derivatives show promising biological activities.⁵⁸ While these derivatives clearly hold great potential in organic synthesis, a careful examination of the literature reveals a lack of methods for their preparation. The conventional route to prepare **MeQone-NH₂³** derivatives is the sequential nitration/reduction of **MeQone-OH⁴** into **MeQone-NH₂³OH⁴**. However, the protocol is limited to substrates having a C-4 hydroxy substituent. Fortunately, an efficient copper-catalyzed *in situ* C(sp²)-NH₂ bond formation to provide a range of **MeQone-NH₂³** from **MeQone-Br³** has been achieved. The reaction conditions involve the use of copper powder as the catalyst, sodium azide as the amine source in the presence of pipecolic acid as the ligand and ascorbic acid as the additive (Table 1.3.2).⁵⁹

Table 1.3.2 Reduction of 3-bromoquinolones

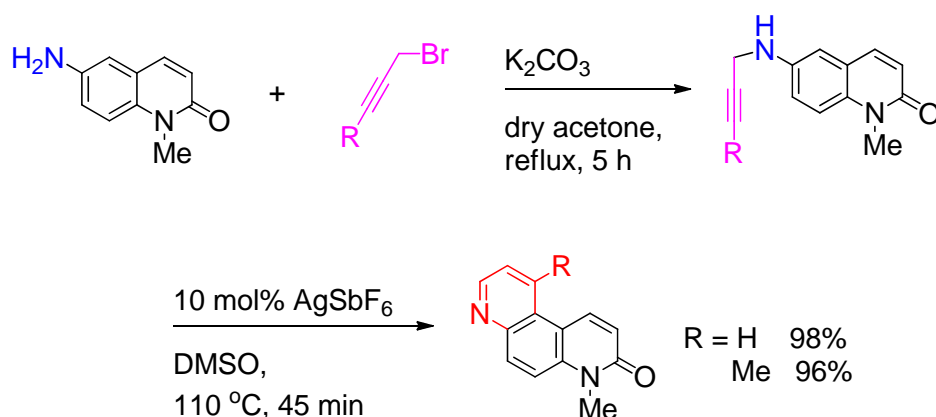


R ¹	R ²	R ³	Yield/%
H	H	H	98
H	H	OMe	98
Ph	H	H	96
H	H	Br	56
H	Br	OMe	65

1.3.9 Cyclization of MeQone-NH₂⁶

The quinolone derivatives have gained considerable attention due to their central role as building blocks in the synthesis of natural products. There are many alkaloids containing pyridoquinolone skeleton, due to the presence of these cores the alkaloids are also bioactive. Traditional approaches have frequently been employed for the synthesis of quinolone ring system in the total synthesis of quinolone based alkaloids. However, all these reactions usually require harsh conditions, tedious reaction procedure, or give poor yield.

Thus, a novel and efficient method for the regioselective synthesis of pyrido[3,2-*f*]quinolone derivatives has been developed. The present method involves propargylation of the 6-amino group, silver-catalyzed 6-*endo*-dig cycloisomerization and aromatization, which proceeds smoothly and provides products in excellent yield (Scheme 1.3.10).⁶⁰

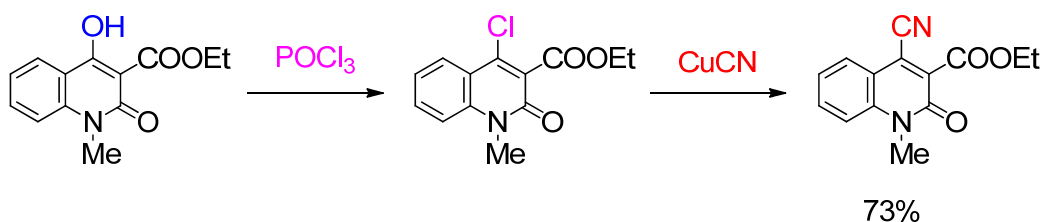


Scheme 1.3.10 Cycloisomerization of MeQone-NH₂⁶

1.3.10 Cyanation of MeQones

Aromatic nitriles are often applied as dyes, herbicides, agrochemicals, and pharmaceuticals. In addition, they are also extremely useful intermediates for organic synthesis, mainly for the formation of heterocycles. A cyano group in organic compounds can undergo various reactions such as hydrolysis, reduction, and elimination. These reactions have been improved to increase the product yield, to reduce waste, and to avoid harsh reaction conditions.

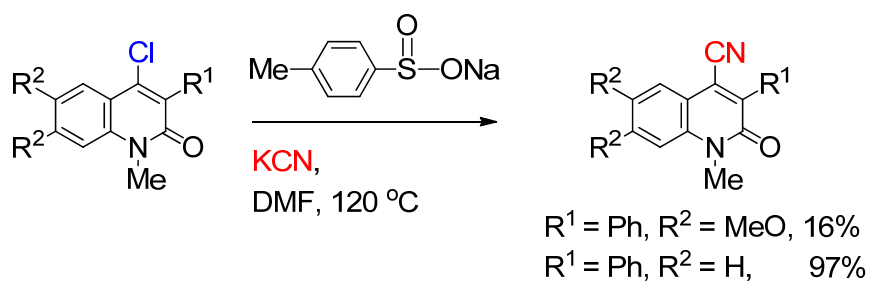
Traditional methods for preparing aromatic nitriles from the corresponding aryl iodides/bromides or aryl diazonium salts are the Rosenmund-von Braun⁶¹ and Sandmeyer reaction,⁶² respectively. These reactions require a stoichiometric amount of CuCN at an elevated temperature, and involve complicated work-up procedures. The other industrial method of choice is amino oxidation, whereby the corresponding toluene derivatives are treated with oxygen and ammonia at 330-550 °C in the presence of a heterogeneous catalyst under high pressure.⁶³



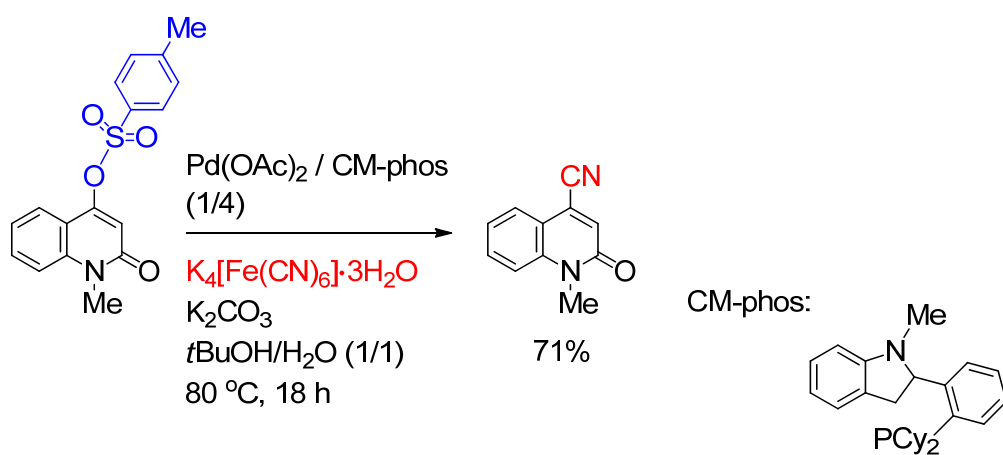
Scheme 1.3.11 Cyanation from MeQone-OH⁴

Recently, halogenation and cyanation of MeQone-OH⁴ are described (Scheme 1.3.11).⁶⁴ In addition, sodium *p*-toluenesulfinate is investigated as the intermediate sulfinate for cyanation of the corresponding aryl halides and potassium cyanide in one-pot (Scheme 1.3.12).³⁰ Moreover, the palladium-catalyzed cyanation of

intermediate aryl tosylates have also been studied (Scheme 1.3.13).⁶⁵ In these synthetic methods, complex catalyst, severe reaction conditions, or a leaving group at the 4-position is necessary.



Scheme 1.3.12 Cyanation of **MeQones-Cl**⁴



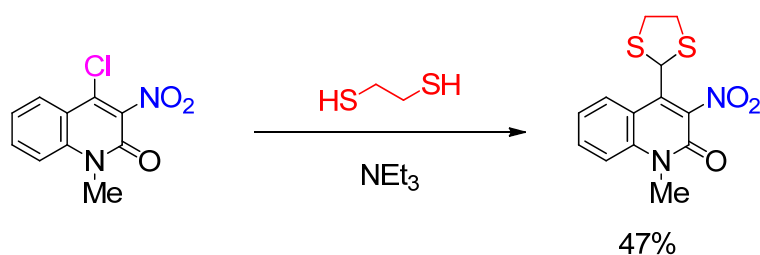
Scheme 1.3.13 Palladium-catalyzed cyanation of **MeQone-OTs**⁴

1.4 Reactivity of Nitrated 1-Methyl-2-quinolones

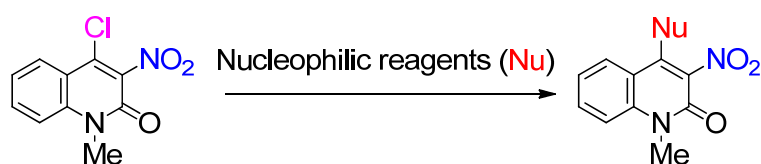
1.4.1 Activation of the vicinal position by a nitro group

The electron-withdrawing ability of the nitro group corresponds to those of two chloro groups, which strongly activates the attached framework. The vicinal position of the nitro group is especially electron-deficient because of its both electron-withdrawing inductive and resonance effects.

When the nitro group is substituted at the 3-position of **MeQone** with a chloro group at the 4-position, it is highly active for the nucleophilic substitution giving 4-functionalized 3-nitroquinolones. By this method, functional groups such as fluoro, alkoxy, amino, azide, alkylthio groups, and malonates are introduced at the 4-position (Table 1.4.1).^{56,66,67} In addition, intramolecular conjugate addition proceeds to afford spiro thioacetal when ethanedithiol is used as the nucleophile (Scheme 1.4.1).⁶⁸

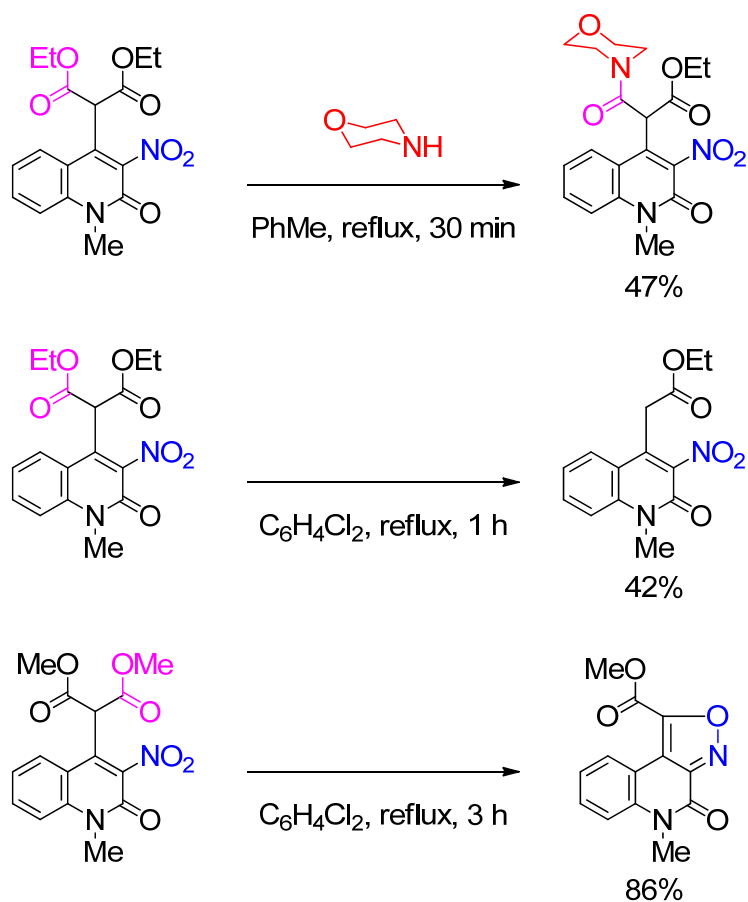


Scheme 1.4.1 Tandem addition of ethanedithiol leading to a spiro compound

Table 1.4.1 Nucleophilic substitution of 4-chloro-3-nitroquinolone

Nucleophilic reagent	Nu	Yield/%	Nucleophilic reagent	Nu	Yield/%
KF / 18-Crown-6	F	95	PhNH ₂	PhNH	98
MeONa	MeO	85	PhCH ₂ NH ₂	PhCH ₂ NH	94
PhOH / K ₂ CO ₃	PhO	93	piperidine	piperidino	96
EtSH / NEt ₃	EtS	95	CH ₂ (COOMe) ₂ / K ₂ CO ₃	CH(COOMe) ₂	95
PhSH + pyridine	PhS	96	CH ₂ (COOEt) ₂ / K ₂ CO ₃	CH(COOEt) ₂	94
NaN ₃	N ₃	95	AcCH ₂ COOEt / K ₂ CO ₃	AcCHCOOEt	90
NH ₃	NH ₂	91	NCCH ₂ COOEt / K ₂ CO ₃	NCCHCOOEt	95

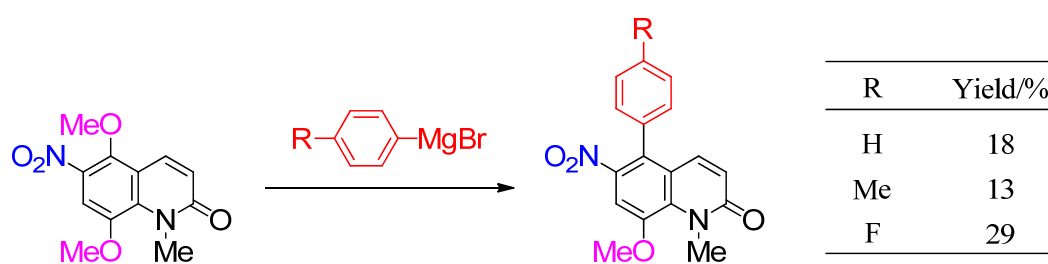
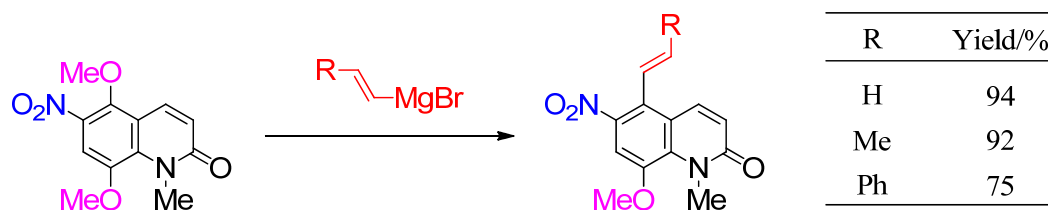
Although malonates are not so reactive under usual conditions, reactivity is improved when they are substituted on the **MeQone** ring. An unsymmetrical amide ester is readily formed upon treatment of quinolylmalonate with morpholine.⁵⁶ Interestingly, the reactivity of quinolylmalonate varies with the alkoxy group of the ester function. While dealkoxycarbonylation proceeds in the case of diethyl ester, an isoxazole ring is constructed on the [*c*]-face in the case of the dimethyl ester (Scheme 1.4.2).⁶⁷



Scheme 1.4.2 Chemical transformation of malonylquinolones

Furthermore, when the nitro group is introduced at the 6-position, activation of the 5-position functional group is also available. For example, when 5,8-dimethoxy-6-nitroquinolone is subjected to reaction with vinyl/aryl Grignard reagents, the arylation proceeds (Table 1.4.2).^{69,70}

Table 1.4.2 Substitution with Grignard reagents

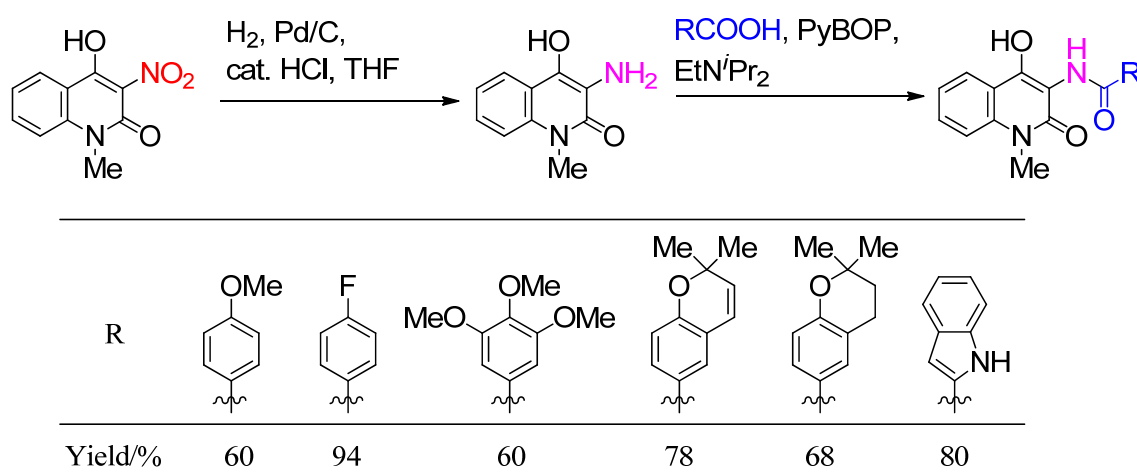


1.4.2 Chemical transformation of a nitro group

Nitro compounds are versatile precursors for diverse functionalities. Their conversion into carbonyl compounds by the Nef reaction and conversion into amines by reduction are the most widely used processes in organic synthesis using nitro compounds. In addition, dehydration of primary nitro compounds leads to nitrile oxides, a class of reactive 1,3-dipolar reagents. Nitro compounds are also good precursor for various nitrogen derivatives such as nitriles, oximes, hydroxylamines, and imines. These transformations of nitro compounds are well established and are used routinely in organic synthesis.

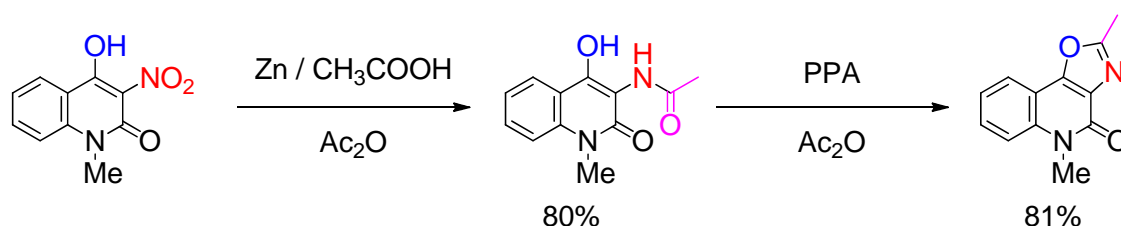
The **MeQone-NO₂³OH⁴** could be reduced by palladium catalyzed hydrogenation, followed by amidation with aromatic acids to obtain 3,4-substituted aminoquinolone derivatives with antikinestoplastid activities (Table 1.4.3).⁷¹

Table 1.4.3 Chemical transformation of a nitro group



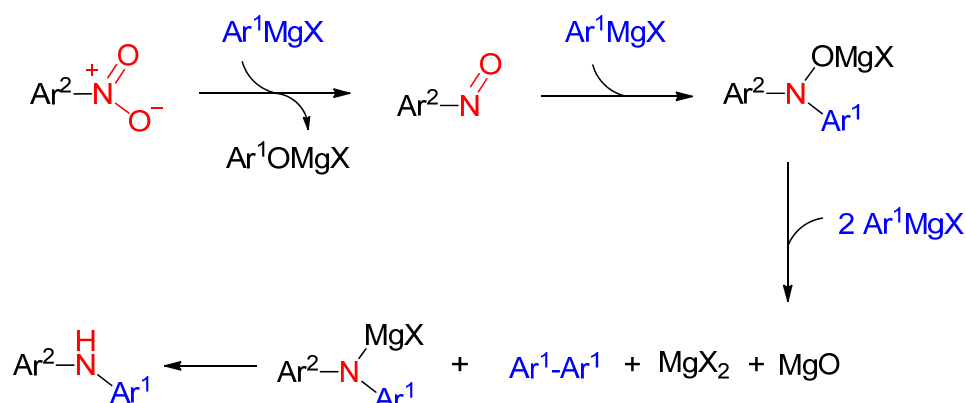
Moreover, the vicinal functions of **MeQone-NO₂³OH⁴** are also used for construction of a fused ring on the [c]-face. When the nitro group is reduced with zinc in acetic acid

in the presence of acetic anhydride, an 3-acetylamino derivative is formed, whose acetyl group protects the sensitive amino group. The subsequent ring closure proceeds by heating in acetic anhydride with polyphosphoric acid at 150 °C to give an isoxazolo[4,5-*c*]quinolone (Scheme 1.4.3).⁷²



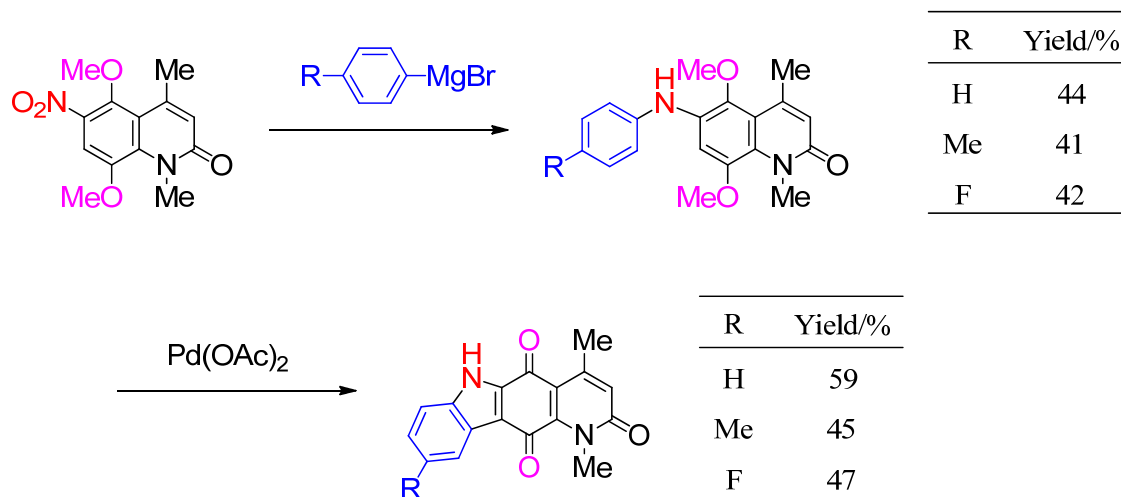
Scheme 1.4.3 Construction of the [*c*]-fused isoxazole ring.

A nitro group on the aromatic ring reacts with aryl Grignard reagents to afford diarylamines via hydroxylamine species (Scheme 1.4.4). 5,8-Dimethoxy-6-nitro-2-quinolone reacts with aryl Grignard to furnish 6-arylamino derivatives, in addition to the substitution at the 5-position mentioned in the previous section (Table 1.4.4). The subsequent treatment of the product with palladium acetate causes successive oxidative coupling and demethylation to afford pyrido[3,2-*b*]carbazolequinones whose intercalating properties are expected to result in antitumor activity.^{70,73}



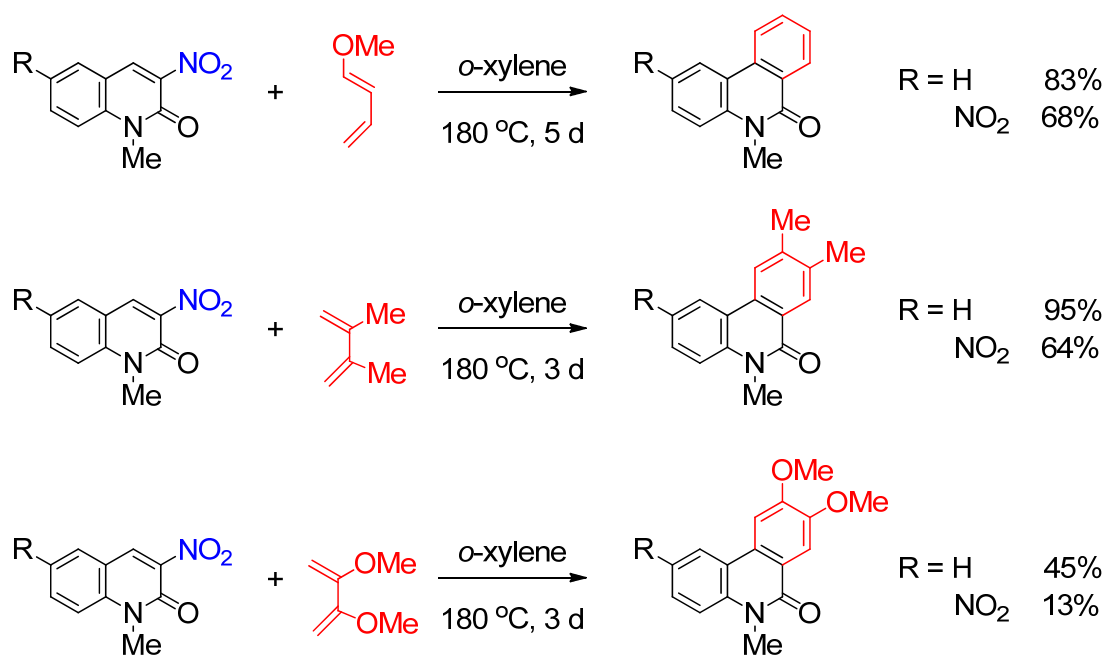
Scheme 1.4.4 Reaction of nitroarene and aryl Grignard reagent

Table 1.4.4 Arylamination of the 6-nitro group followed by conversion to pyridocarbazole



1.4.3 Cycloaddition of nitroalkene moiety

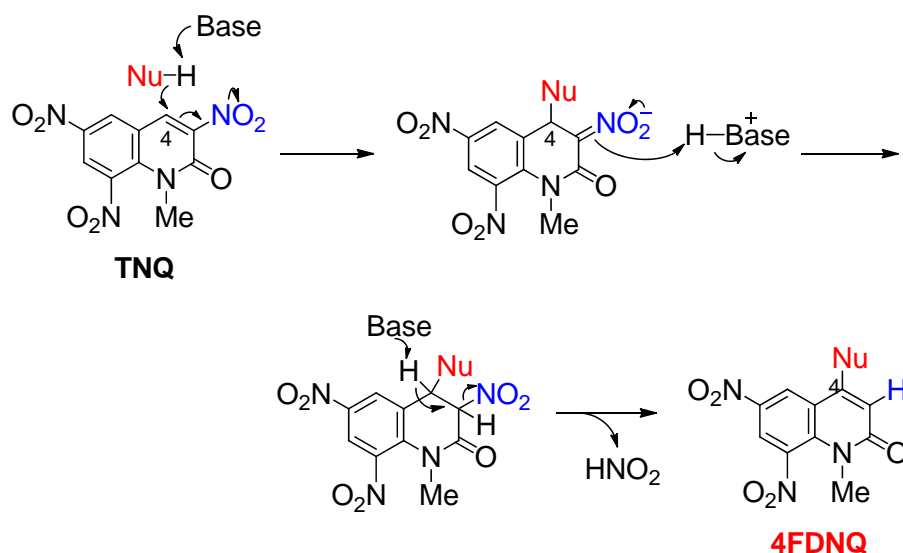
MeQones having a nitro group at the 3- or the 4-position serve as nitroalkenes that undergo Diels-Alder reactions with electron-rich dienes leading to benzoquinoline derivatives, in which the constructed ring aromatizes accompanied by elimination of nitrous acid (Scheme 1.4.5). Although this methodology enables simultaneous C-C bond formation at the 3- and 4-positions of the **MeQone** framework, severe reaction conditions must be employed.^{74,75} To the contrary, trinitroquinolone (**TNQ**) quite easily undergoes cycloaddition under mild conditions as detailed in the next section.



Scheme 1.4.5 Diels-Alder reactions of 3-nitroquinolones

1.5 High Reactivity of 1-Methyl-3,6,8-trinitro-2-quinolone

In our research, we have focused on the chemistry of nitrated **MeQones**, especially 1-methyl-3,6,8-trinitro-2-quinolone (abbreviated as **TNQ**),⁷⁶ and used as the key precursor for versatile functionalized **MeQone** derivatives. **TNQ** exhibits significantly high reactivity, which is unusual compared with other nitroquinolones. Indeed, **TNQ** reacts with versatile nucleophiles to undergo *cine*-substitution. First the nucleophilic substitution proceeds at the 4-position of **TNQ** to form adduct intermediate, then the proton from basic group is transferred to the 3-position of adduct intermediate affording 3,4-dihydroquinolone. As a result of elimination of the vicinal nitro group, 4-substituted 6,8-dinitro-1-methyl-2-quinolones (**4FDNQ**) are formed (Scheme 1.5.1).⁷⁷ This reaction enables the functionalization at the 4-position of **TNQ** with forming a C-C or a C-N bond regioselectively.



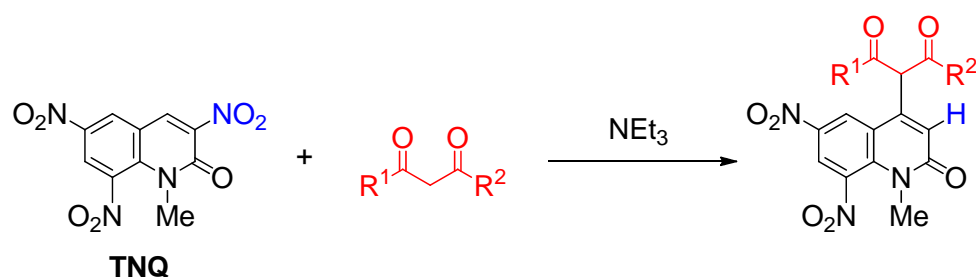
Scheme 1.5.1 *cine*-Substitution of **TNQ** with nucleophiles

1.5.1 *cine*-Substitution with carbon nucleophiles

The *cine*-substitution reactions of **TNQ** with carbon nucleophiles, including 1,3-dicarbonyl compounds, nitroalkanes, aldehydes/ketones, enamines and phenoxides, are useful protocol for regioselectively forming a C-C bond at the 4-position leading to versatile skeletons.

1,3-Dicarbonyl compounds such as β -diketones, β -keto esters and β -diesters easily react with **TNQ** in the presence of triethylamine at room temperature to afford **4FDNQs** (Table 1.5.1).⁷⁶

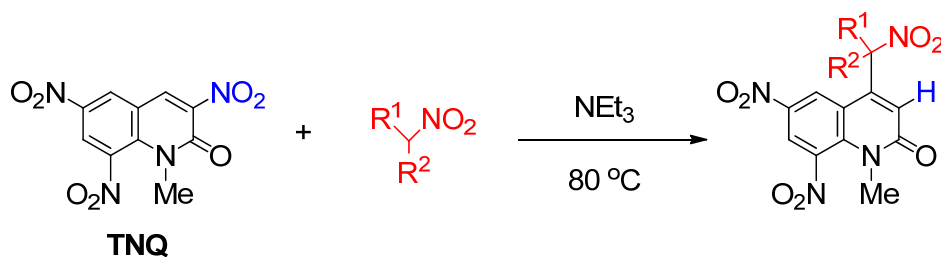
Table 1.5.1 Reactions of **TNQ** with 1,3-dicarbonyl compounds



R^1	R^2	Yield/%
CH_2COOEt	OEt	26
$-(CH_2)_3-$		60
Me	Me	88
Me	OEt	93
OEt	OEt	99

Nitroalkylation is performed upon treatment of **TNQ** with nitroalkane as a C-H acid (Table 1.5.2).⁷⁸ While primary nitroalkanes undergo the *cine*-substitution efficiently, secondary nitroalkanes are less reactive, requiring longer reaction time.

Table 1.5.2 Reactions of **TNQ** with nitroalkanes

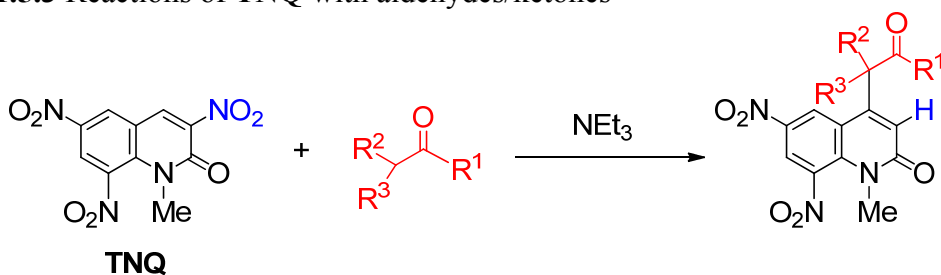


R ¹	R ²	Yield/%
Me	H	80
Et	H	98
Me	Me	77

Acylmethylation of **TNQ** is also performed directly by conducting reactions of **TNQ** with ketones in the presence of triethylamine. This reaction is applicable to aliphatic, alicyclic, aromatic, and heteroaromatic ketones (Table 1.5.3).⁷⁹ Since the acylmethyl group is expected to serve as a scaffold for further chemical transformations, this method would be useful for construction of a new libraries of compounds having a **MeQone** framework.

In the reaction of **TNQ** with enamines, morpholinium salts of 3,4-dihydroquinolones are formed, in which intermediate iminium ions are hydrolyzed and deprotonation at the 3-position by the liberated morpholine proceeds (Table 1.5.4).⁷⁹

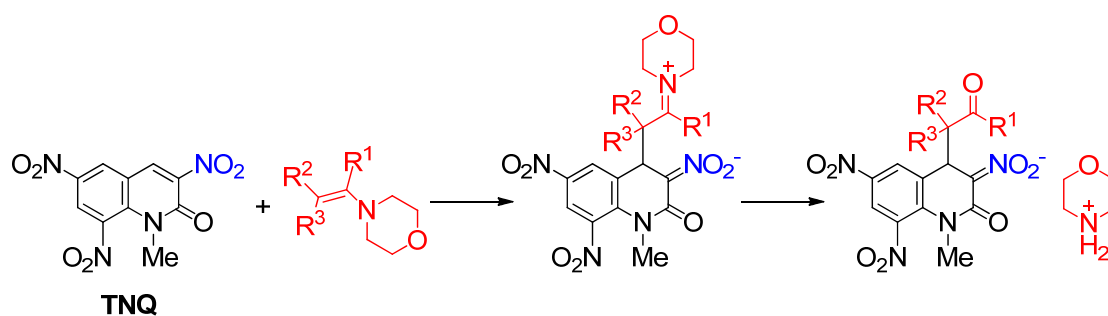
Table 1.5.3 Reactions of **TNQ** with aldehydes/ketones



R ¹	R ²	R ³	Yield/%
H	Me	Me	41
2-Furyl	H	H	45
2-Pyridyl	H	H	74
Me	H	H	83
Ph	H	H	83
Et	Me	H	18
Ph	Ph	H	69
Ph	Me	H	77
-(CH ₂) ₄ -		H	82

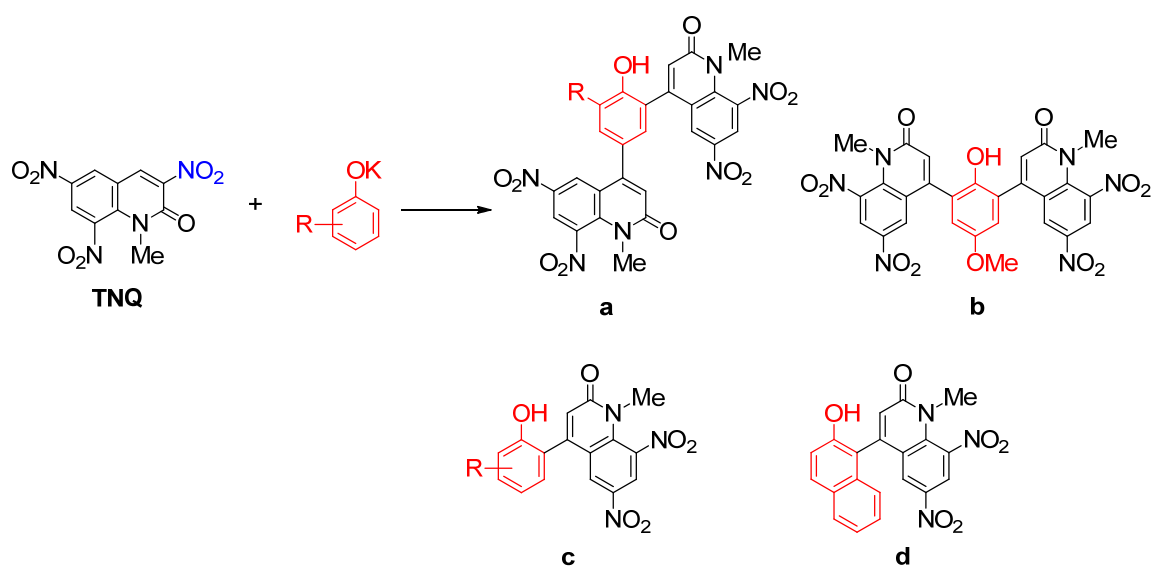
Direct arylation of the **MeQone** is one of the more useful modifications from a viewpoint of further functionalization; however, it is quite difficult because the accompanying destruction of the aromaticity of both quinolone and benzene rings. This difficulty is overcome when a combination of electrophilic **TNQ** and nucleophilic phenoxide ions is employed. While phenol, 2-methylphenol, and 4-methoxyphenol undergo double substitution to afford bis(quinolyl)phenols, bulky or electron-poor phenoxides give monoquinolylphenols as a sole product (Table 1.5.5).⁸⁰

Table 1.5.4 Reactions of **TNQ** with enamines



R ¹	R ²	R ³	Yield/%
-(CH ₂) ₃ -		H	40
Ph	Me	H	43
Ph	Ph	H	98
H	Me	Me	98

Table 1.5.5 Reactions of TNQ with phenoxides

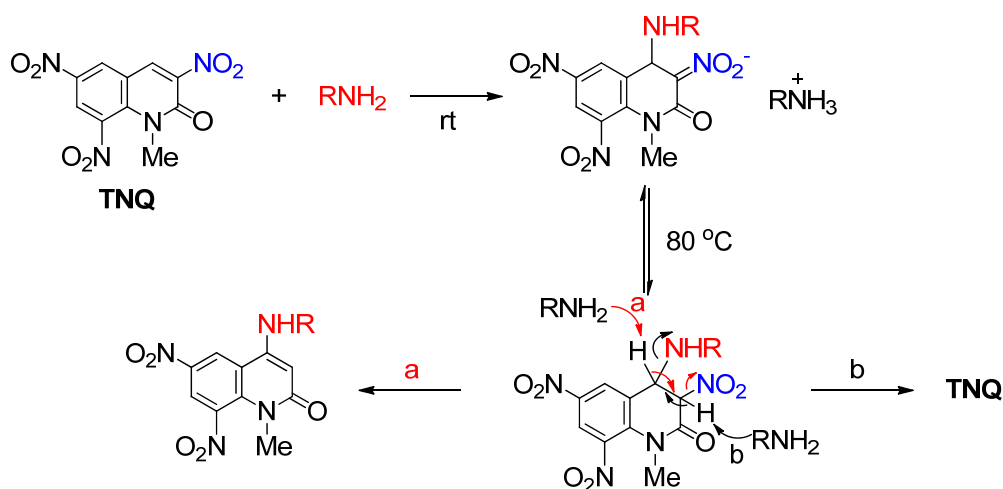


R	Product	Yield/%
H	a	51
2-Me	a	91
4-MeO	b	67
3-Me	c	35
4-Me	c	82
4-NO ₂	c	36
<i>o</i> -Phenylene	d	75

1.5.2 *cine*-Substitution with amines

When amines as the nucleophiles are reacted with **TNQ**, a C-N bond is formed at the 4-position. The conjugate addition of primary amines readily occurs at the 4-position of **TNQ**, and the resulting adduct is converted to an ammonium salt by another molecule of amine. When the salt is heated, a small amount of *cine*-substituted product is formed, together with recovery of a large amount of **TNQ**. In this reaction, 3,4-dihydroquinolone is formed under equilibrium at reflux temperature, from which the former product is afforded by deprotonation at the 4-position via **route a**, and the latter product is a result of deprotonation at the 3-position via **route b** (Table 1.5.6).⁸¹

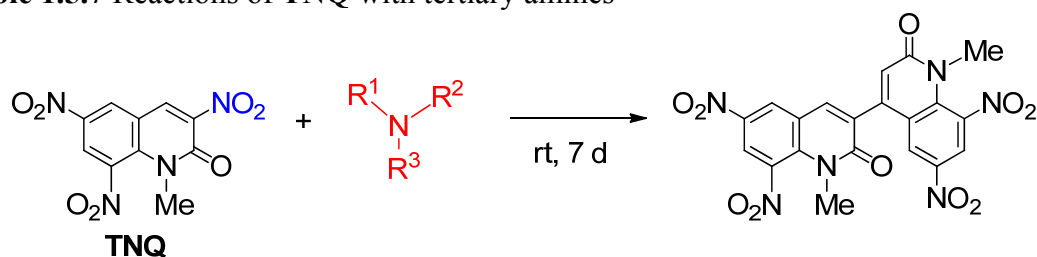
Table 1.5.6 Reactions of **TNQ** with primary amines



R	Yield/%	
	ammonium salt	<i>cine</i> -substituted product
Pr	71	36
<i>i</i> -Bu	74	29
<i>s</i> -Bu	56	0
<i>t</i> -Bu	74	0

On the other hand, dimerization proceeds in the reaction of **TNQ** with less nucleophilic tertiary amines, by which the dimer connected between the 3- and the 4'-positions is formed. The reaction rate is significantly affected by the length and the number of alkyl chains of the amine (Table 1.5.7). Namely, tributylamine causes the reaction faster than tripropylamine and triethylamine, and no reaction proceeds in the cases of trimethylamine and tribenzylamine. In addition, more than two long alkyl chains are necessary for the reaction to occur efficiently.⁸²

Table 1.5.7 Reactions of **TNQ** with tertiary amines

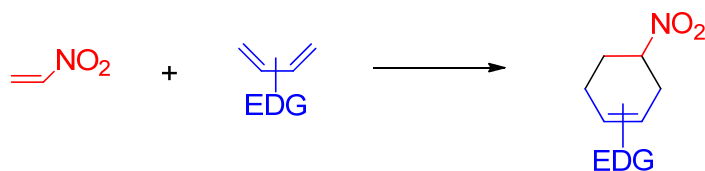


R ¹	R ²	R ³	Yield/%
Me	Me	Bu	18
Et	Et	Et	34
Pr	Pr	Pr	76
Bu	Bu	Me	79
Bu	Bu	Bu	93

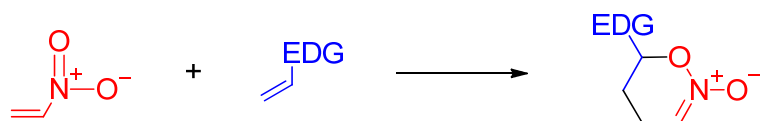
1.5.3 Cycloaddition of TNQ

Nitro compounds have been converted into various cyclic compounds via cycloaddition reactions. In particular, nitroalkenes have proved to be useful in Diels-Alder reactions. Under thermal conditions, they behave as electron-deficient dienophiles and react with dienes to yield 3-nitrocyclohexenes. Nitroalkenes can also act as heterodienes and react with olefins in the presence of Lewis acids to yield cyclic alkyl nitronates, which undergo the [3+2] cycloaddition (Scheme 1.5.2).⁸³⁻⁸⁶ Nitro compounds are precursors for nitrile oxides, alkyl nitronates, and trialkylsilyl nitronates, which undergo the [3+2] cycloaddition reactions. Thus, nitro compounds play important roles in the chemistry of cycloaddition reactions.

(a) as a dienophile



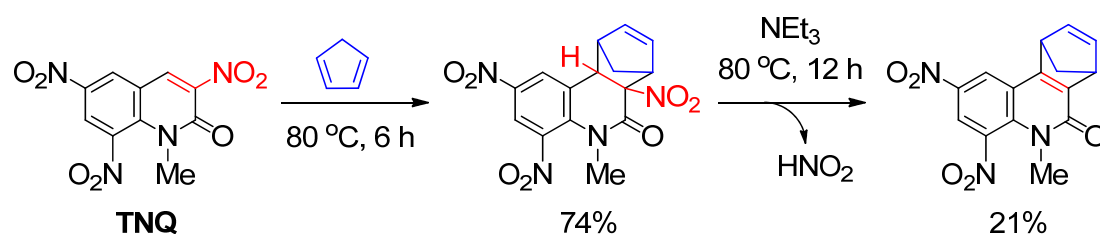
(b) as a heterodiene



Scheme 1.5.2 Dual reactivity of nitroalkene in the cycloaddition

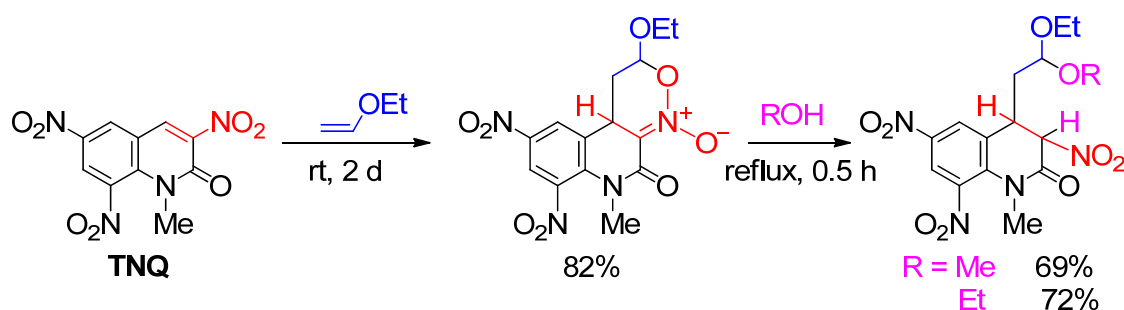
Diels-Alder reactions are one of the most fundamental and useful reactions in synthetic organic chemistry. Various dienes and dienophiles have been employed for this useful reaction, in which nitroalkenes take part in Diels-Alder reactions in various ways. As mentioned in last section, the pyridone moiety of **TNQ** reveals nitroalkene

properties rather than aromaticity, which means that the C₃-C₄ moiety could cause cycloaddition under mild conditions, compared with Diels-Alder reactions of 3-nitroquinolone and 3,6-dinitroquinolone with electron-rich dienes require quite severe conditions.^{74,75} Indeed, efficient cycloaddition proceeds leading to tetracyclic compounds when **TNQ** is allowed to react with cyclopentadiene at 80 °C (Scheme 1.5.3).⁸⁷ The cycloadduct aromatizes with elimination of nitrous acid upon treatment with triethylamine.



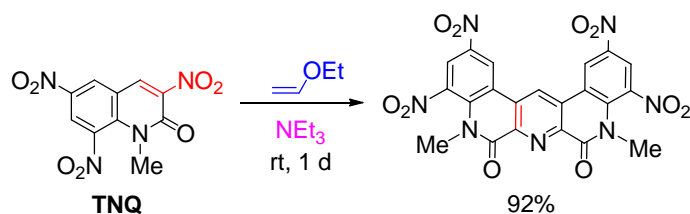
Scheme 1.5.3 Diels-Alder reaction of **TNQ** with cyclopentadiene

On the other hand, the nitroalkene moiety of **TNQ** also serves as a heterodiene in the reaction with ethoxyethene to construct a fused oxazine ring. The cycloadduct is easily converted to an acetal by the ring opening reaction upon heating in alcohol (Scheme 1.5.4).⁸⁸

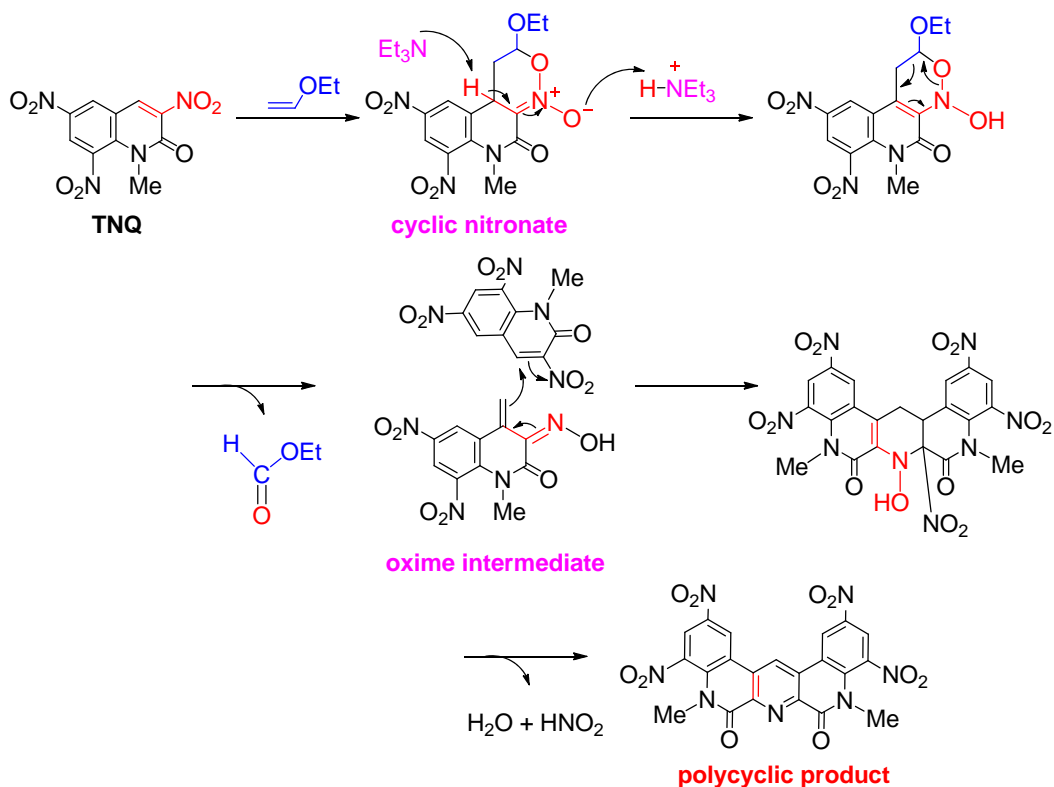


Scheme 1.5.4 Cycloaddition of **TNQ** with ethoxyethene in the absence of NEt₃

Moreover, a quinolino[3,4-*b*][1,9]diazaphenanthrene derivative is formed when the same substrates are treated in the presence of triethylamine. A plausible mechanism for the construction of polycyclic product is illustrated in Scheme 1.5.5.⁸⁸ The reaction is initiated by cycloaddition of **TNQ** with ethoxyethene affording a cyclic nitronate. Then, triethylamine accelerates the prototropy from the pyridone ring to the oxygen atom of the nitronate, followed by a retro-Diels-Alder reaction occurs to give the α,β -unsaturated oxime with a loss of ethyl formate. The cycloaddition of oxime intermediate with another molecule of **TNQ** constructs a new pyridine ring, and the subsequent aromatization furnishes the polycyclic product together with elimination of one nitrous acid and water.

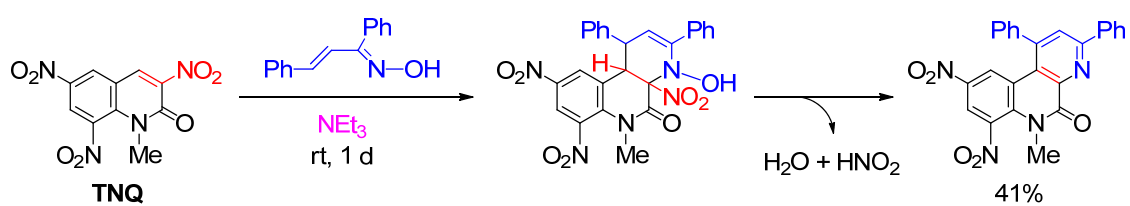


Plausible reaction mechanism:



Scheme 1.5.5 Cycloaddition of **TNQ** with ethoxyethene in the presence of NEt_3

In the present process, the former intermediate oxime behaves as an electron-rich heterodiene and the latter **TNQ** behaves as an electron-poor dienophile. This mechanism is supported by the experimental fact that polycyclic diazaphenanthrene is isolated in a moderate yield as a result of cycloaddition of **TNQ** with α,β -unsaturated oxime as the electron-rich heterodiene (Scheme 1.5.6).⁸⁸



Scheme 1.5.6 Cycloaddition of **TNQ** with α,β -unsaturated oxime

1.6 Research Purpose

The functionalization of the **MeQone** skeleton is not easily performed due to somewhat aromaticity of the pyridone moiety, so it is highly demanded to develop new synthesis and functionalization methods for the **MeQone** framework involving easy experimental manipulations under mild conditions.

On the other hand, a variety of unnatural **MeQone** derivatives are easily prepared from nitroquinolones, in which the nitro groups in the **MeQone** framework are efficiently activated to undergo the chemical transformations. Especially, **TNQ** exhibits unusually high reactivity. When **TNQ** is treated with nucleophilic reagents, *cine*-substitution proceeds to form a C-C or C-N bond at the 4-position regioselectively. Moreover, polycyclic compounds having the **MeQone** framework as a partial structure are readily prepared by cycloadditions using the nitroalkene properties of **TNQ**. Nitroquinolones are useful scaffolds for constructing a library of **MeQone** derivatives, and are expected to exhibit new reactivity in the future.

In this thesis, molecular design and synthesis of quinolones activated by steric effect between the 1-methyl and 8-substituent groups will be studied, which can be applied for synthesis and functionalization of versatile **MeQone** derivatives with latent bioactivity.

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Chapter 2 *cine*-Substitution of Nitroquinolones

2.1 Introduction

While the pyridone moiety of *N*-unsubstituted quinolone shows high aromaticity because of its tautomeric quinolinol structure, the pyridone moiety of *N*-methylquinolone (**MeQone**) cannot have such tautomeric structure. However, the **MeQone** also shows slight aromaticity, which is due to the contribution of the betaine resonance structure (Figure 2.1.1). The aromatic property of the **MeQone** diminishes the reactivity to prevent the direct nucleophilic and/or electrophilic functionalization. Hence, development of simple functionalizing methods for the **MeQone** framework is one of the significant subjects, which is highly useful for construction of a compound library of **MeQone** derivatives.

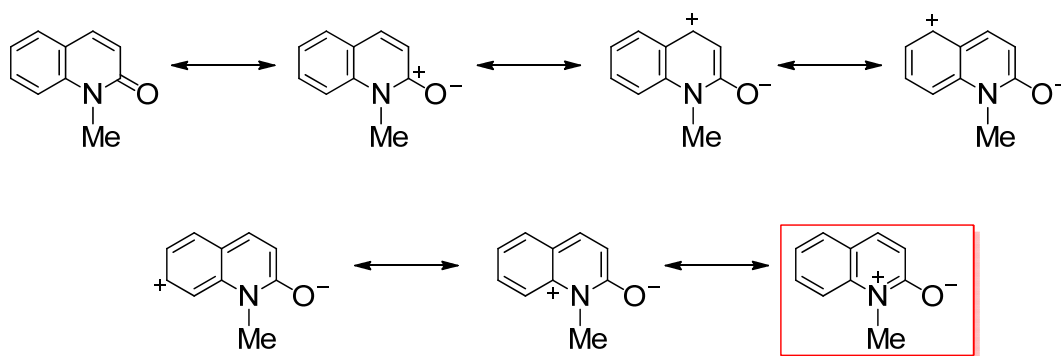
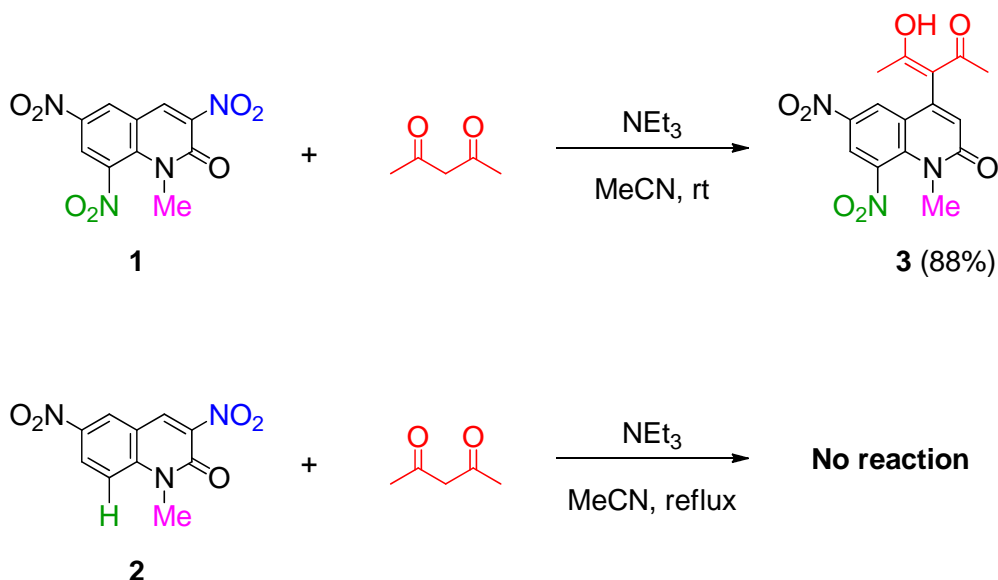


Figure 2.1.1 Resonance structures for **MeQone**

Meanwhile, we have found that 1-methyl-3,6,8-trinitro-2-quinolone (**1**) exhibited high reactivity compared with other **MeQone** derivatives.¹ Indeed, when quinolone **1** was treated with 2,4-pentanedione in the presence of triethylamine at room temperature, the *cine*-substitution proceeded efficiently to afford 4-functionalized

6,8-dinitro-2-quinolone **3**.² To the contrary, 1-methyl-3,6-dinitro-2-quinolone (**2**) caused no change even at an elevated temperature (Scheme 2.1.1).³ These results suggest that both 1-methyl and 8-nitro groups are necessary for the high reactivity of quinolone **1**.

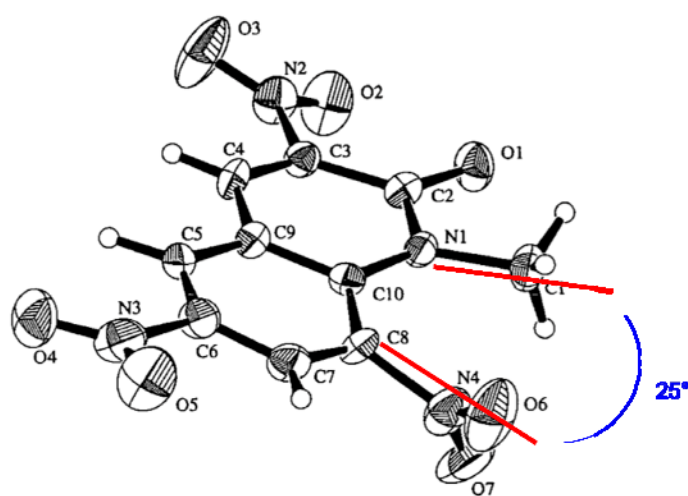


Scheme 2.1.1 Reaction of nitrated 1-methyl-2-quinolones with 2,4-pentanedione

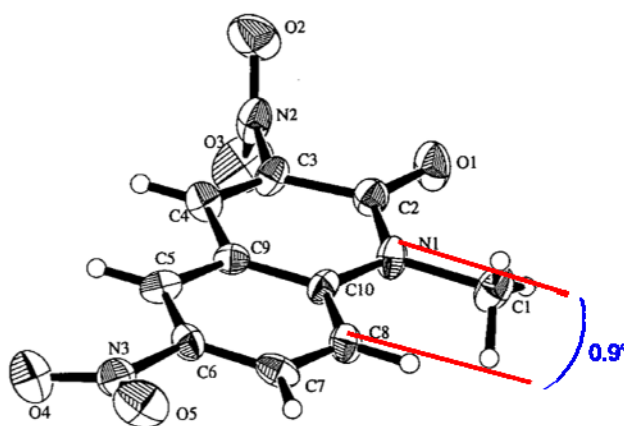
The quite different reactivity between the quinolones **1** and **2** cannot be rationalized by only electron-withdrawing effect of the 8-nitro group. Thus, the structural difference was estimated by MOPAC (PM3) molecular orbital calculations. While quinolone **2** reveal that the benzene and pyridone rings present are almost coplanar, in which the dihedral angle between the N₁-Me and C₈-R⁸ was 0.9°. On the other hand, the 2-quinolone ring of **1** is torsionally strained by the steric compression of the 1-methyl and the 8-nitro groups, in which the corresponding dihedral angle bonds was 25.0°. The X-ray analysis of **1** and **2** well corresponds to the calculated results (Figure 2.1.2). Moreover, the 8-nitro group of quinolone **1** has no coplanarity with the scaffold, which turns through 67.7°, which interferes the conjugation to prevent from serving as an

electron-withdrawing group by resonance effect.

As a result of disturbing the coplanarity, the pyridone moiety serves as an activated nitroalkene rather than an aromatic species because of lacking effective overlapping of π -orbitals,⁴ which should be a major reason for the extremely high reactivity of quinolone **1**. This hypothesis prompted us to study the activation of the **MeQone** framework sterically by a substituent at the 8-position.



(a) Quinolone 1



(b) Quinolone 2

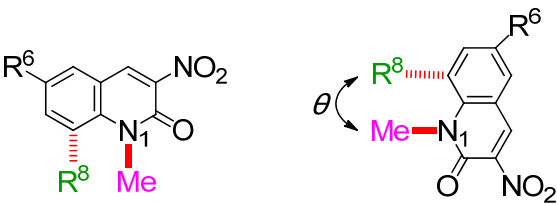
Figure 2.1.2 ORTEP views of quinolones **1** (a) and **2** (b)

2.2 Results and Discussion

2.2.1 Prediction of steric distortion by DFT calculation

In the last section, it is supposed that high reactivity of quinolone **1** is caused by steric repulsion between the 1-methyl and the 8-nitro groups. In other words, the high reactivity remains even though one of the three nitro groups is exchanged by a methyl group. In order to confirm this consideration, distortion degrees of four kinds of nitroquinolones **1**, **2**, **4** and **5** are estimated by density functional theory (DFT) calculation using B3LYP/6-31+G(d,p). The calculated dihedral angles between two bonds, N₁-Me and C₈-R₈, are shown in Table 2.2.1.

Table 2.2.1 Dihedral angles between N₁-Me and C₈-R₈ bonds



Compound	R ⁶	R ⁸	Dihedral angles θ
1	NO ₂	NO ₂	29.0°
2	NO ₂	H	1.5°
4	Me	NO ₂	29.2°
5	NO ₂	Me	30.9°

While the dihedral angle of trinitroquinolone **1** is 29.0°, that of 1-methyl-3,6-dinitro-2-quinolone **2** is 1.5°, which means that the benzene and the pyridone moieties are almost coplanar. This result is similar to the calculated one using MOPAC (PM3). The dihedral angles of quinolones **4** and **5**, are also calculated similarly. These are the structures that one of the three nitro groups is exchanged by a methyl

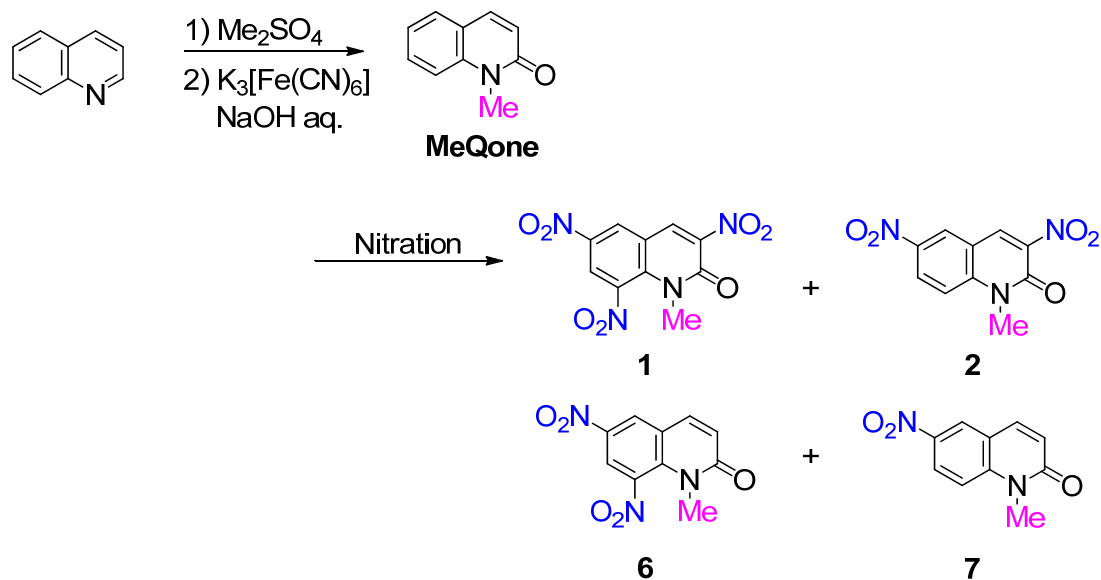
group. Dihedral angles for 1,6-dimethyl-3,8-dinitro-2-quinolone (**4**) and 1,8-dimethyl-3,6-dinitro-2-quinolone (**5**) are 29.2° and 30.9°, respectively. These values are similar to that of quinolone **1**, which implies that both quinolones **4** and **5** should reveal high reactivity as well as **1**.

2.2.2 Preparation of nitrated 2-quinolones

A. Nitration of 1-methyl-2-quinolone

When **MeQone** was nitrated with 15 M nitric acid under medium temperature, mono- and di-nitrated **MeQones** are main products (Table 2.2.2, entries 1-3). On the other hand, when **MeQone** was nitrated with 15 M nitric acid under higher temperature, quinolone **1** is the only product (entry 4). Furthermore, the use of fuming acid instead of 15 M nitric acid under higher temperature could afford quinolone **1** in a higher yield (entry 5).⁵ On the basis of these results, the nitro group is introduced following the order of 6- > 3- \approx 8-positions, in which nitration at the 3-position is somewhat easier than at the 8-position.

Table 2.2.2 Preparation of nitroquinolones from quinoline



Entry	Nitration reagent	Temp./ °C	Time/h	Yield/%			
				1	2	6	7
1	HNO ₃ /H ₂ SO ₄	50	5	0	0	0	72
2	HNO ₃ /H ₂ SO ₄	70	5	4	26	10	19
3	HNO ₃ /H ₂ SO ₄	80	5	8	41	29	18
4	HNO ₃ /H ₂ SO ₄	120	7	63	0	0	0
5	fuming HNO ₃	120	7	90	0	0	0

B. Nitration of 1,6-dimethyl-2-quinolone

The starting 1,6-dimethyl-2-quinolone (**9**)⁶ was prepared from commercially available 6-methylquinoline (**8**) according to the synthetic method reported for 1-methyl-2-quinolone (**MeQone**).⁷

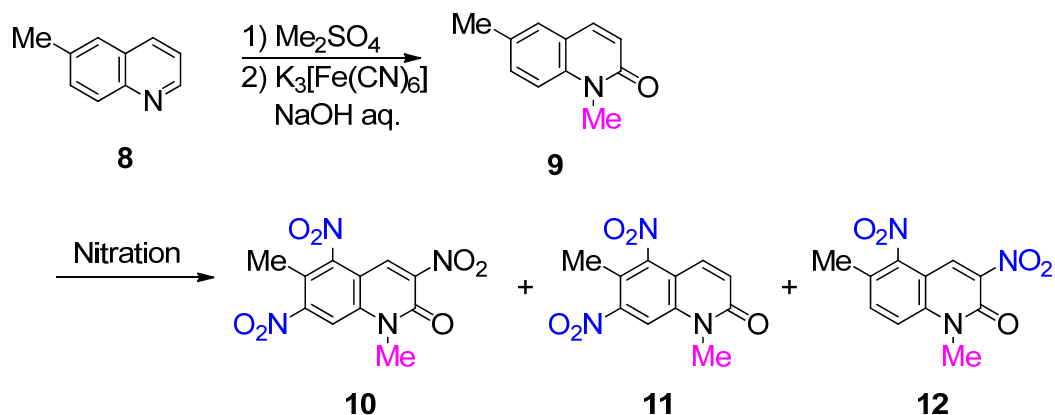
In the nitration of 1,6-dimethyl-2-quinolone (**9**), the nitro groups were mainly introduced at the 5- and the 7-positions as well as at the 3-position, in which the electron-donating 6-methyl group serves as an *ortho*-directing group. Moreover, the steric hindrance of 1-methyl group prevented the nitration at the 8-position.

In the ¹H NMR of 1,6-dimethyl-3,5,7-trinitro-2-quinolone (**10**), only two signals were observed at 8.55 and 8.69 ppm, in addition to two methyl group singlets, 2.42 and 3.40 ppm, which means three nitro groups are introduced at the 3, 5 and 7-positions of 1,6-dimethyl-2-quinolone (**9**).

In the case of 1,6-dimethyl-5,7-dinitro-2-quinolone (**11**), a couple of doublets with coupling constant 10.0 Hz were observed in the higher field, 6.92 and 7.74 ppm, which are assigned to protons on the pyridone ring. Thus, it is considered to be two nitro groups at the 5 and 7-positions.

In the ¹H NMR of 1,6-dimethyl-3,5-dinitro-2-quinolone (**12**), two nitro groups were similarly introduced at the 3 and 5-positions because of a couple of doublets with coupling constant 9.2 Hz revealed at 7.72 and 7.81 ppm.

For these results, when 1,6-dimethyl-2-quinoline (**9**) is directly nitrated. Although the desired 3,8-dinitroquinolone **4** was not detected in the reaction mixture, three kinds of nitrated 1,6-dimethyl-2-quinolones **10**, **11** and **12** were obtained upon nitration of 1,6-dimethyl-2-quinolone (**9**).

Table 2.2.3 Optimization for nitration of 1,6-dimethyl-2-quinolone

Entry	Nitrating reagent	Temp./°C	Time/h	Yield/%		
				10	11	12
1	HNO ₃ /H ₂ SO ₄	50	24	16	21	45
2	HNO ₃ /H ₂ SO ₄	80	5	11	11	5
3	HNO ₃ /H ₂ SO ₄	80	24	33	49	0
4	fuming HNO ₃	120	7	10	0	0

The optimization of reaction conditions was studied, and results were shown in Table 2.2.3. At lower temperature, dinitroquinolones **11** and **12** were mainly obtained (entry 1). Heating for longer reaction time increased yields of products **10** and **11** (entries 2 and 3). On the other hand, only small amount of trinitroquinolone **10** was obtained in the nitration using fuming HNO₃ (entry 4). This might be due to the decomposition of substrate/product under harsh conditions, and due to the formation of some polar products easily soluble into water, which lowered yields of nitro quinolones. On the basis of these experimental results, the nitro groups are found to be introduced in the order of 5- > 3- ≈ 7-positions.

C. Nitration of 1,8-dimethyl-2-quinolone

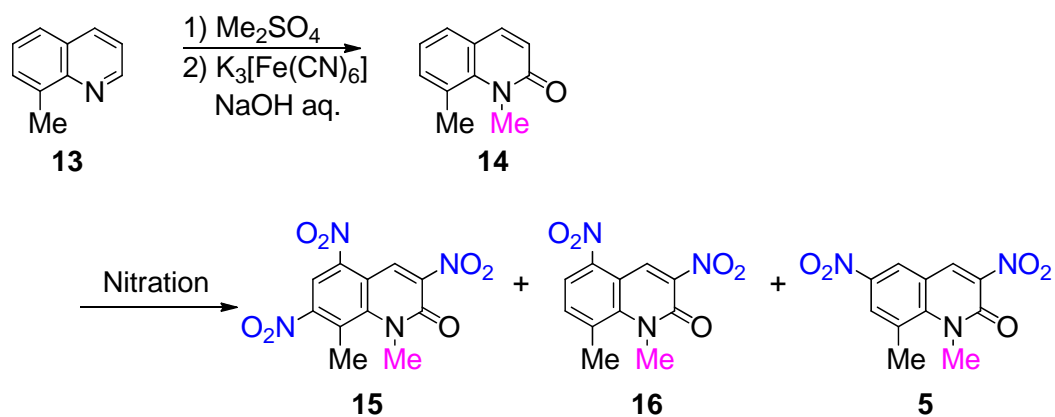
The starting 1,8-dimethyl-2-quinolone (**14**)⁶ was also prepared from commercially available 8-methylquinoline (**13**) according to the synthetic method reported for **MeQone**.⁷

In the case of the nitration of 1,8-dimethyl-2-quinolone (**14**), firstly the nitro groups were mainly introduced at 5- and 7-positions with 8-methyl group served as a stronger *ortho*, *para*-direction group than the acylamino group (the ring nitrogen) to afford 1,8-dimethyl-3,5,7-trinitro-2-quinolone (**15**), 1,8-dimethyl-3,5-dinitro-2-quinolone (**16**) as the products. Then, the acylamino group (the ring nitrogen) also served as a *para*-directing group at the 6-position to give the desired 1,8-dimethyl-3,6-dinitro-2-quinolone (**5**).

Structural determination of nitrated products was performed as follows. In the ¹H NMR spectrum of trinitroquinolone **15**, only two singlet signals were observed at 8.53 and 8.60 ppm, which means three nitro groups are introduced at the 3-, the 5-, and the 7-positions of **14**.

In the case of nitroquinolone **16**, a couple of doublets with coupling constant 9.6 Hz was observed at 6.92 and 7.66 ppm. Furthermore, COSY and NOESY spectra also supported the position of a nitro group to be the 5-position, which is the *para*-position of the 8-methyl group.

In the ¹H NMR of quinolone **5**, a couple of doublets was observed in the lower field, 8.42 and 8.80 ppm, with coupling constant 2.8 Hz, which means the ring nitrogen of pyridone moiety activated the 6-position as a *para*-directing group.

Table 2.2.4 Optimization for nitration of 1,8-dimethyl-2-quinolone

Entry	Nitrating reagent	Temp./°C	Time/h	Yield/%		
				15	16	5
1	HNO ₃ /H ₂ SO ₄	50	12	12	47	28
2	HNO ₃ /H ₂ SO ₄	50	24	27	40	28
3	HNO ₃ /H ₂ SO ₄	80	5	trace	39	0
4	HNO ₃ /H ₂ SO ₄	80	24	45	17	0
5	fuming HNO ₃	120	24	31	0	0

The reaction conditions were optimized, and results were shown in Table 2.2.4. Similar to nitration of 1,6-dimethyl-2-quinolone (**9**), dinitroquinolones **16** and **5** were obtained in moderate yields (entries 1 and 2). Moreover, when 1,8-dimethyl-2-quinolone (**14**) is nitrated with shorter time, nitro groups are introduced in the order of 5- ≈ 3- > 7- > 6-positions (entry 3). In reactions at higher temperature and with longer time, trinitroquinolone **15** was afforded as a main product (entries 4 and 5).

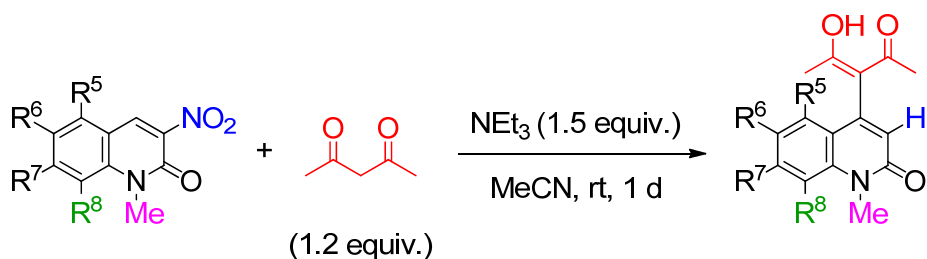
2.2.3 *cine*-Substitution of nitrated dimethyl-2-quinolones with 2,4-pentanedione

When the remain quinolone **1** was treated with 2,4-pentanedione at room temperature, the *cine*-substitution proceeded efficiently to afford 4-functionalized 6,8-dinitro-2-quinolone **3** in 88% yield (Table 2.2.5, entry 1).²

To the contrary, when 1-methyl-3,6-dinitro-2-quinolone (**2**) with a hydrogen at the 8-position was treated with 2,4-pentanedione in the presence of triethylamine, the *cine*-substitution did not proceed even at an elevated temperature (entry 2).³ Similarly, 1,6-dimethyl-3,5,7-trinitro-2-quinolone (**10**) also caused no change because of no substituent at the 8-position (entry 3), which prove that the steric repulsion between the 1-methyl group and the 8-nitro group activate the **MeQone** framework.

On the other hand, when the nitroquinolones **15** and **16** with a nitro group at the 5-position were subjected to the reactions with 2,4-pentanedione in the presence of triethylamine, neither nitroquinolones **15** nor **16** caused reaction (entries 4 and 5) under the same conditions. I suppose that the *peri*-substituent (R^5) might prevent the approach of the bulky enolate of 2,4-pentanedione to the 4-position despite the presence of a methyl group at the 8-position.

Table 2.2.5 *cine*-Substitution of nitrated dimethyl-2-quinolones with 2,4-pentanedione



Entry	R ⁵	R ⁶	R ⁷	R ⁸	Nitroquinolones	Products	Yield/%
1	H	NO ₂	H	NO ₂	1	3	88
2	H	NO ₂	H	H	2	17	0
3	NO ₂	Me	NO ₂	H	10	18	0
4	NO ₂	H	NO ₂	Me	15	19	0
5	NO ₂	H	H	Me	16	20	0
6	H	NO ₂	H	Me	5	21	92

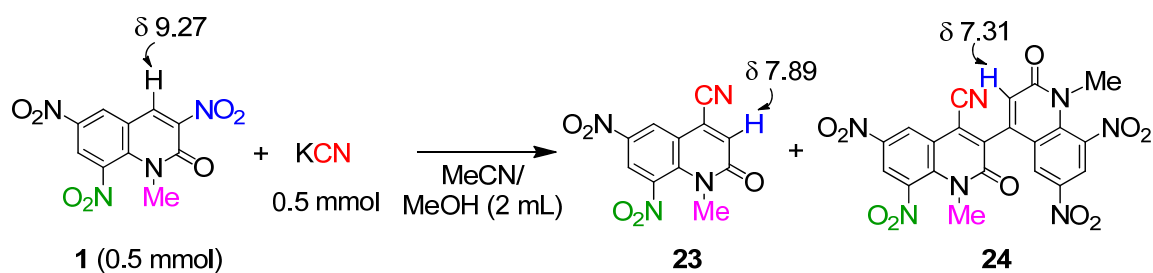
It is noteworthy that *cine*-substitution efficiently proceeded to afford product **21** in 92% yield when the substrate **5** was employed, which has only two nitro groups (entry 6). This experimental fact strongly supported the hypothesis: the steric repulsion between two methyl groups activates the **MeQone** framework as mentioned in Section 2.1.

2.2.4 *cine*-Substitution of 1-methyl-3,6,8-trinitro-2-quinolone with potassium cyanide

In order to estimate the activating effect of the steric repulsion between the substituents at the 1- and the 8-positions, it is necessary to employ a small nucleophile instead of a bulky enolate of 2,4-pentanedione to avoid the steric hindrance of a substituent at the 5-position. From this viewpoint, cyanide was employed as a nucleophile. When a solution of potassium cyanide in methanol was added to a solution of the quinolone **1** in acetonitrile, and heated at 60 °C for 2 h, a complex mixture was obtained, from which two products, the 4-cyano-2-quinolone derivative **23** and the dimeric product **24** were isolated.

In the ¹H NMR of products **23** and **24**, singlet signals at 7.89 ppm and 7.31 ppm, respectively, which considerably shifted to the higher field from 9.27 ppm observed for trinitroquinolone **1**. These spectral changes reveal that both compounds are *cine*-substituted products, and their structures were determined to be the 4-cyano-2-quinolone derivative **23** and the dimeric product **24** on the basis of spectral and analytical data.

The reaction conditions were optimized as shown in Table 2.2.6. The reaction temperature was found to be a crucial factor for the present reaction. When the temperature was lowered to 0 °C, the total yield of **23** and **24** was increased up to 94% (the yield of **23** was increased up to 80%), accompanied with the simplification of the reaction mixture (entries 1-4). On the other hand, a longer reaction time did not affect the yields of **23** and **24** (entry 5).

Table 2.2.6 Optimization of reaction conditions

Entry	Temp./ °C	Solv./mL	Time/h	Yield/% ^a		Total yield/%	Recovery of 1 /%
				23	24		
1	60	20	2	63	9	72	7
2	rt	20	2	73	7	80	7
3	0	20	2	80	14	94	6
4	-20	20	2	78	10	88	11
5	0	20	4	69	9	78	6
6	0	10	2	71	7	78	9
7	0	50	2	62	7	69	8
8 ^b	0	20	2	73	14	87	9

^aDetermined by ¹H NMR based on quinolone **1**;

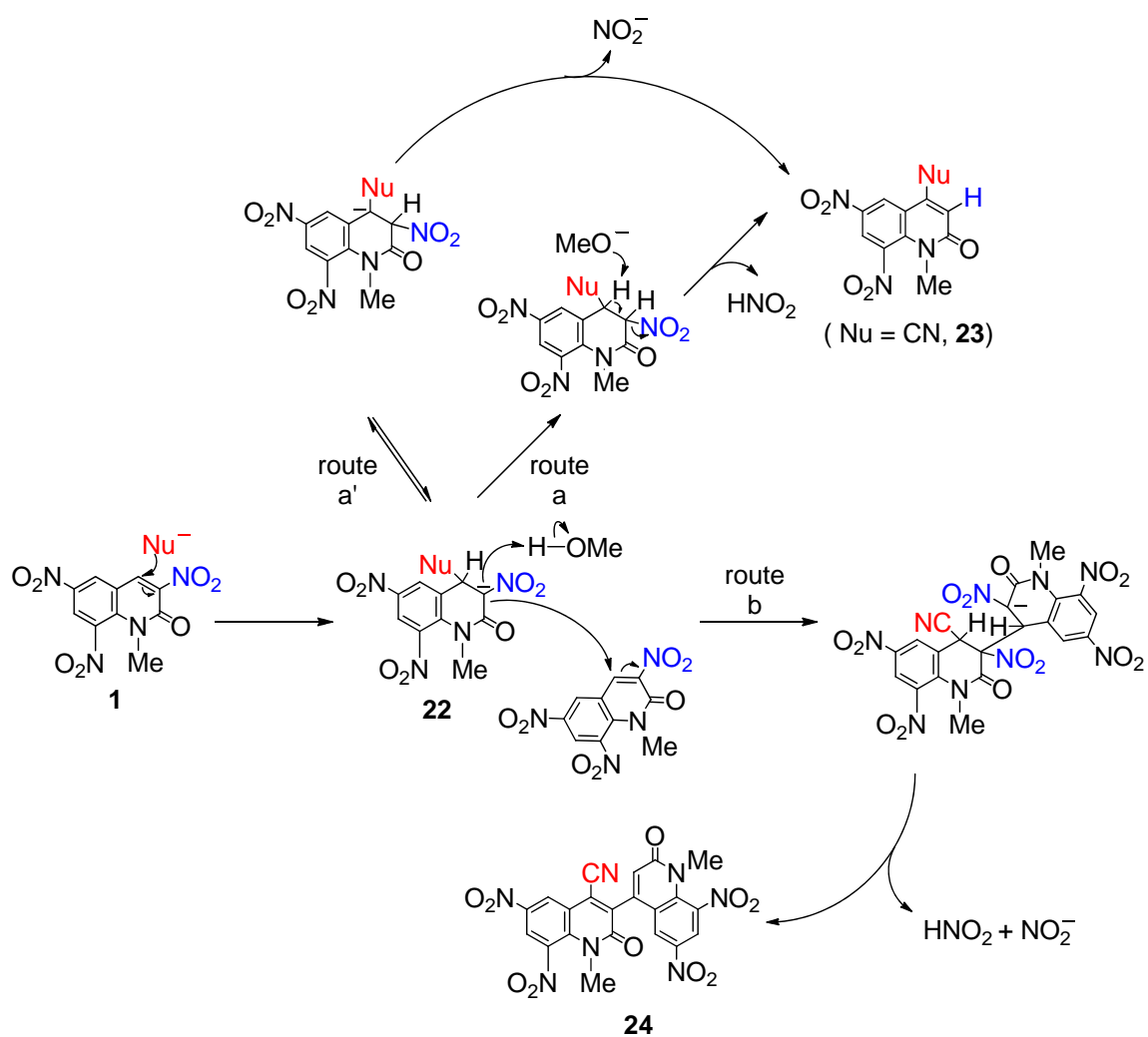
^bH₂O was used as the solvent in order to completely dissolve KCN.

Next, the control of the reaction routes was attempted by changing the volume of solvent. When the reaction was conducted under concentrated conditions, many other signals than those of **23** and **24** were observed in the reaction mixture without considerable change in the ratio of **23/24** (entry 6). Moreover, dilution was not so effective for avoiding the dimerization (entry 7). The solvent effect for the reaction was also investigated; when water was employed as the solvent for dissolving potassium cyanide, many by-products were observed (entry 8). Hence, methanol was more suitable solvent for dissolving potassium cyanide, which was somewhat influential for inhibiting the side reactions during the whole reaction process.

2.2.5 A plausible reaction mechanism

A plausible mechanism for forming these products is illustrated in Scheme 2.2.1. The reaction is initiated with the nucleophilic attack of cyanide ($\text{Nu} = \text{CN}$) at the 4-position of quinolone **1**. Cyanoquinolone **23** is afforded when the resultant anion **22** is protonated, followed by the elimination of a nitrous acid molecule (route a). Another route is also acceptable, which involves the proton migration followed by elimination of nitrite anion (route a').

On the other hand, the dimeric product **24** is formed when the intermediate anion **22** attacks another molecule of quinolone **1**, and the pyridone moieties aromatize accompanied by the elimination of nitrous acid molecules (route b). Although this kind of dimerization was observed in the reaction of quinolone **1** with tertiary amines,⁵ this is the first example to isolate a dimer in the reaction with a C-nucleophile. The strongly electron-withdrawing ability of the carbonyl and nitro groups by resonance effect is considered to stabilize the anionic intermediate **22**.

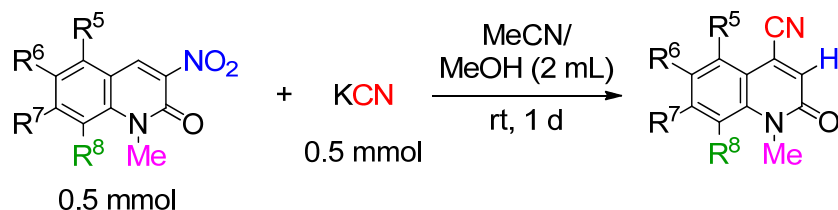


Scheme 2.2.1 A plausible reaction mechanism for the formation of **23** and **24**

2.2.6 *cine*-Substitution of nitrated 1,8-dimethyl-2-quinolones with potassium cyanide

The *cine*-substitution reactions of nitrated 1,8-dimethyl-2-quinolones with potassium cyanide were investigated (Table 2.2.7). Although the 3,5,7-trinitroquinolone **15** caused no change upon treatment with 2,4-pentanedione, the reaction with potassium cyanide efficiently proceeded to afford the *cine*-substituted product 4-cyanoquinolone **25**, in 83% yield (entry 2). The cyanation also occurred to afford product **26** even when the 3,5-dinitroquinolone **16** was employed (entry 3). Furthermore, the 3,6-dinitroquinolone **5** revealed high reactivity to undergo the *cine*-substitution quantitatively to give product **27** (entry 4). These results strongly supported our consideration that the steric repulsion between 1-methyl and 8-methyl groups activated the **MeQone** by disturbing the coplanarity (entries 3 and 4).

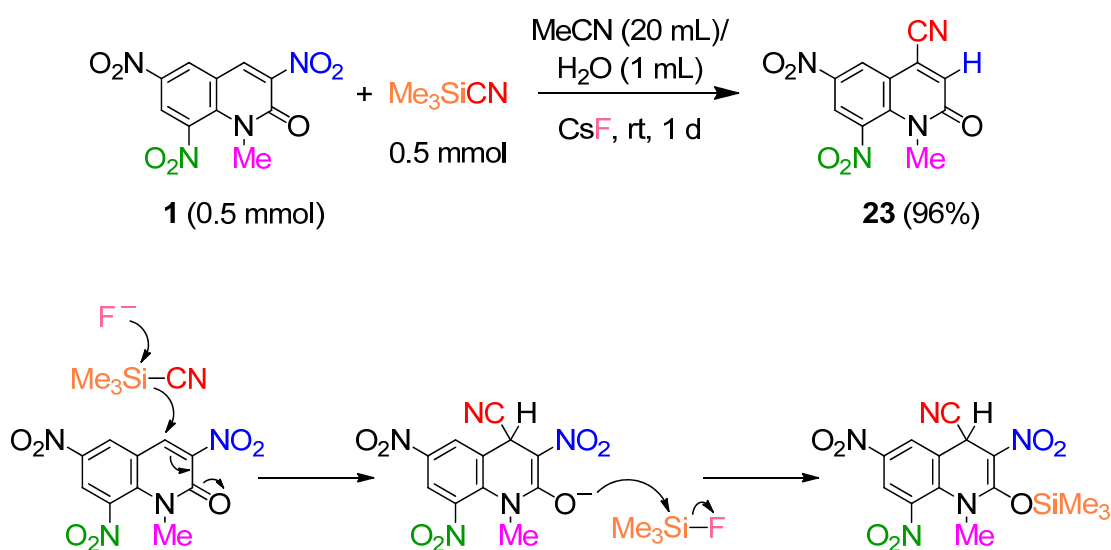
Table 2.2.7 *cine*-Substitution of nitrated 1,8-dimethyl-2-quinolones with KCN



Entry	R ⁵	R ⁶	R ⁷	R ⁸	Nitroquinolone	Product	Yield/%
1	H	NO ₂	H	NO ₂	1	23	73
2	NO ₂	H	NO ₂	Me	15	25	83
3	NO ₂	H	H	Me	16	26	47
4	H	NO ₂	H	Me	5	27	quant.

2.2.7 *cine*-Substitution of 1-methyl-3,6,8-trinitro-2-quinolone with trimethylsilyl cyanide

Finally, in order to investigate the cation effect of cyanide compounds, trimethylsilyl cyanide/cesium fluoride was employed instead of potassium cyanide. To our expectation, the formation of the dimer **24** was not observed, and the yield of **22** dramatically increased up to 96%, when the reaction was conducted at room temperature for 1 day (Scheme 2.2.2). I suppose that the anionic intermediate is trapped by a trimethylsilyl group to afford a silyl enol ether, by which the nucleophilicity of the enolate was lost, and consequently the attack of enolate to another molecular of quinolone **1** was prevented.



Scheme 2.2.2 *cine*-Substitution of quinolone **1** with trimethylsilyl cyanide

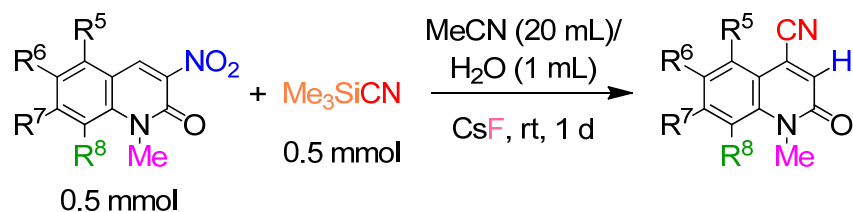
While known cyanation methods of the **MeQone** framework require multi-step reactions or severe conditions,⁸⁻¹³ the present method enables the cyanation through shorter synthetic schemes. This advantageous feature will make the present method as a

useful synthetic tool for constructing a library of versatile **MeQone** derivatives by the further chemical conversion of the cyano and nitro functionalities.

2.2.8 *cine*-Substitution of nitrated 1,8-dimethyl-2-quinolones with trimethylsilyl cyanide

The *cine*-substitution reactions of nitrated 1,8-dimethyl-2-quinolones with trimethylsilyl cyanide were also investigated (Table 2.2.8). Because of the steric hindrance of 5-nitro group prevents the approach to the 4-position, when trinitroquinolone **15** was reacted with trimethylsilyl cyanide, only small amount of *cine*-substituted product **25** formed, no reaction proceeded in the case of dinitroquinolone **16** (entries 2 and 3). On the other hand, the 3,6-dinitroquinolone **5** revealed high reactivity to undergo the *cine*-substitution quantitatively to afford product **27** (entry 4).

Table 2.2.8 *cine*-Substitution of nitrated 1,8-dimethyl-2-quinolones with trimethylsilyl cyanide



Entry	R ⁵	R ⁶	R ⁷	R ⁸	Nitroquinolone	Product	Yield/%
1	H	NO ₂	H	NO ₂	1	23	96
2	NO ₂	H	NO ₂	Me	15	25	42
3	NO ₂	H	H	Me	16	26	0
4	H	NO ₂	H	Me	5	27	quant.

2.3 Conclusions

A simple method for the cyanation of a nitrated **MeQones** having a substituted at the 8-position has been developed. When 8-position was substituted with nitro group, *cine*-substitution and dimerization easily proceeded under mild reaction conditions to afford the cyanoquinolones **23** and **24**. The reaction could be used as an estimating tool for the activation degree of the **MeQone** framework. As a result, the presence of an 8-substituent was found to be crucial for causing the *cine*-substitution, which activated the **MeQone** framework by steric repulsion with the 1-methyl group. These results should be useful information for functionalization of the **MeQone** framework by activating sterically, and are helpful for finding new biologically active compounds.

2.4 Experimental Section

2.4.1 General information

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. TLC was performed using Merck silica gel 60 F254, and column chromatography was performed using silica gel 60 (Nacalai Tesque, spherical neutral, 150 μ m). The ^1H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The mass spectra and the high resolution mass spectra were measured on a JEOL JMS-DX303HF.

2.4.2 Preparation of 1-methyl-3,6,8-trinitro-2-quinolone **1**

Following the procedure described for 1-methyl-2-pyridone⁷ to prepare 1-methyl-2-quinolone: To quinoline (5.41 mL, 45.8 mmol) in 300 mL flask, dimethyl sulfate was added dropwise during 10 min. After addition, the mixture was heated at 60 °C for 30 min, and then 15 mL H₂O was added to obtain reddish 1-methylquinolinium ion solution. Under ice bath, potassium ferricyanide (32.28 g, 98 mmol) solution (128 mL H₂O) and sodium hydroxide (8.04 g, 201 mmol) solution (26 mL H₂O) were added dropwise into flask during 1 h. After addition, the reaction mixture was stirred at room temperature for 30 min and filtrated. The filtrate was extracted with CHCl₃ (50 mL × 3). The organic layer was dried with anhydrous MgSO₄, filtrated and concentrated. At last, the residue was extracted with hexane (30 mL × 8) under reflux conditions and the hexane extract was concentrated to afford 1-methyl-2-quinolone (**MeQone**, 5.832 g, 36.7 mmol, 80%) as a yellow solid.

Nitration of 1-methyl-2-quinolone to prepare 1-methyl-3,6,8-trinitro-2-quinolone:⁵ To cold fuming HNO₃ (*d* = 1.52 g/mL, 12 mL, 290 mmol), 1-methyl-2-quinolone (1.7 g, 10.5 mmol) was gradually added and the mixture was heated at 120 °C for 7 h. After the reaction, 100 mL H₂O was poured onto the reaction mixture. Crystalline precipitates were collected and recrystallized from CH₃CN to afford 1-methyl-3,6,8-trinitro-2-quinolone (**1**, 1.996g, 6.8 mmol, 65%) as yellow needles.

2.4.3 Preparation of nitrated 1,6-dimethyl-2-quinolones

In a 300 mL round bottomed flask, dimethyl sulfate was added dropwise during 10 min. to 6-methylquinoline **8** (6.15 mL, 45.8 mmol). After the mixture was heated at 100 °C for 4 h, 15 mL of H₂O was added to furnish reddish 1-methylquinolinium ion solution. On an ice bath, a solution of potassium ferricyanide (32.28 g, 98 mmol) in water (128 mL) and a solution of sodium hydroxide (8.04 g, 201 mmol) in water (26 mL) were added dropwise into flask during 1 h. After addition, the reaction mixture was stirred at room temperature for 30 min. and precipitates were filtered off. The filtrate was extracted with CHCl₃ (50 mL × 3). The organic layer was dried over MgSO₄ and concentrated. The residue was extracted with hexane (30 mL × 8) under reflux conditions and the hexane extract was concentrated to afford 1,6-dimethyl-2-quinolone (**9**, 6.664 g, 38.5 mmol, 84%) as a yellow solid.

To cold 18 M H₂SO₄ (11.1 mL, 200 mmol), the quinolone **9** (1.7 g, 10 mmol) was gradually added and then 15 M HNO₃ (23.3 mL, 350 mmol) was added gradually. The resultant mixture was heated at 50 °C for 1 d. After cooling down to room temperature, H₂O (50 mL) was poured into the reaction mixture. The generated yellow precipitate (2.6 g) was collected by filtration. Further purification was performed by recrystallization or column chromatography on silica gel to afford 1,6-dimethyl-3,5,7-trinitro-2-quinolone (**10**), 1,6-dimethyl-5,7-dinitro-2-quinolone (**11**), and 1,6-dimethyl-3,5-dinitro-2-quinolone (**12**).

2.4.4 Preparation of nitrated 1,8-dimethyl-2-quinolones

To 8-methylquinoline **13** (6.23 mL, 45.8 mmol), dimethyl sulfate was added dropwise during 10 min. After the mixture was heated at 100 °C for overnight, 15 mL of H₂O was added to give a reddish 1-methylquinolinium ion solution. On an ice bath, a solution of potassium ferricyanide (32.28 g, 98 mmol) in water (128 mL) and a solution of sodium hydroxide (8.04 g, 201 mmol) in water (26 mL) were added dropwise during 1 h. After addition, the reaction mixture was stirred at room temperature for 30 min and precipitates were filtered off. The filtrate was extracted with CHCl₃ (50 mL × 3). The organic layer was dried over MgSO₄, and concentrated. The residue was extracted with hexane (30 mL × 8) under reflux conditions and the extract was concentrated to afford 1,8-dimethyl-2-quinolone (**14**, 6.766 g, 38.9 mmol, 85%) as a yellow solid.

To cold 18 M H₂SO₄ (11.1 mL, 200 mmol), the quinolone **14** (1.7 g, 10 mmol) was gradually added and then 15 M HNO₃ (23.3 mL, 350 mmol) was added gradually. The resultant mixture was heated at 50 °C for 12 h. After cooling down to room temperature, H₂O (30 mL) was poured into the reaction mixture. The generated yellow precipitate (2.6 g) was collected by filtration. Further purification was performed by recrystallization or column chromatography on silica gel to afford 1,8-dimethyl-3,5,7-trinitro-2-quinolone (**15**), 1,8-dimethyl-3,5-dinitro-2-quinolone (**16**), and 1,8-dimethyl-3,6-dinitro-2-quinolone (**5**).

2.4.5 *cine*-Substitution of 1,8-dimethyl-3,6-dinitro-2-quinolone with 2,4-pentanedione

To a solution of 1,8-dimethyl-3,6-dinitro-2-quinolone (**5**, 132 mg, 0.5 mmol) and 2,4-pentanedione (61mg, 0.6 mmol) in acetonitrile (20 mL), 0.025 M solution of triethylamine (30 mL, 0.75 mmol) was added at room temperature over 30 min, and the solution color turned to brown. The reaction mixture was stirred for a further 1 d. After concentration, the reaction mixture was dissolved into CHCl₃ (20 mL) and washed with H₂O (20 mL) to remove Et₃NHNO₂. The organic layer was dried over MgSO₄, and concentrated. The residue was purified by recrystallization with hexane to afford *cine*-substituted product **21** (145 mg, 0.46 mmol, 92% yield).

2.4.6 General procedure for 1-methyl-3,6,8-trinitro-2-quinolone with potassium cyanide

To a solution of 1-methyl-3,6,8-trinitro-2-quinolone (**1**, 147 mg, 0.5 mmol) in acetonitrile (20 mL), potassium cyanide (33 mg, 0.5 mmol) was added at 60 °C, and the mixture was stirred for 2 h. Then, the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford the *cine*-substituted product **23** (eluted with hexane/ethyl acetate = 7/3, 87 mg, 0.315 mmol, 63%) and the dimeric product **24** (eluted with hexane/ethyl acetate = 1/1, 12 mg, 0.023 mmol, 9% based on **1**), respectively.

2.4.7 *cine*-Substitution of 1,8-dimethyl-3,5,7-trinitro-2-quinolone with potassium cyanide

To a solution of 1,8-dimethyl-3,5,7-trinitro-2-quinolone (**15**, 154 mg, 0.5 mmol) in acetonitrile (15 mL), a solution of potassium cyanide (33 mg, 0.5 mmol) in MeOH (2 mL) was added at room temperature, and the mixture was stirred for 1 d. Then, the reaction mixture was filtrated, and the filtrate was concentrated under reduced pressure. The residue was recrystallized with MeOH to afford *cine*-substituted product **25** (119 mg, 0.41 mmol, 83% yield).

2.4.8 *cine*-Substitution of 1,8-dimethyl-3,5-trinitro-2-quinolone with potassium cyanide

To a solution of 1,8-dimethyl-3,5-dinitro-2-quinolone (**16**, 132 mg, 0.5 mmol) in acetonitrile (15 mL), a solution of KCN (33 mg, 0.5 mmol) in MeOH (2 mL) was added at room temperature, and the mixture was stirred for 1 d. Then, the solution was concentrated under reduced pressure, and purified with column chromatography to afford *cine*-substituted product **26** (eluted with hexane/ethyl acetate = 3/7, 57 mg, 0.24 mmol, 47% yield).

2.4.9 *cine*-Substitution of 1,8-dimethyl-3,6-trinitro-2-quinolone with potassium cyanide

To a solution of 1,8-dimethyl-3,6-dinitro-2-quinolone (**5**, 132 mg, 0.5 mmol) in acetonitrile (15 mL), a solution of KCN (33 mg, 0.5 mmol) in MeOH (2 mL) was added at room temperature, and the mixture was stirred for 1 d. Then, the solution was concentrated under reduced pressure. Pure *cine*-substituted product **27** (166 mg, 0.5 mmol, quant.) was obtained without further purification.

2.4.10 *cine*-Substitution of nitrated 2-quinolones with trimethylsilyl cyanide

To a solution of nitrated 2-quinolones (0.5 mmol) and trimethylsilyl cyanide (50 mg, 0.5 mmol) in acetonitrile (20 mL), a solution of cesium fluoride (76 mg, 0.5 mmol) in H₂O (1 mL) was added at room temperature, and the mixture was stirred for 1 d and concentrated. Then, the residue was subjected to a measurement of ¹H NMR, and the yield of *cine*-substituted products was calculated using internal standard (Cl₂CHCHCl₂).

2.4.11 Characterization data of products

1-Methyl-3,6,8-trinitroquinolin-2(1H)-one (1): yellow needle; ^1H NMR (400 MHz, DMSO- d_6) δ 3.43 (s, 3H), 9.08 (d, J = 2.8 Hz, 1H), 9.25 (d, J = 2.8 Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 35.2 (CH₃), 120.2 (C), 124.8 (CH), 130.5 (CH), 136.3 (CH), 137.6 (C), 138.5 (C), 140.9 (C), 140.9 (C), 154.4 (CO).

1,6-Dimethylquinolin-2(1H)-one (9): light yellow solid; ^1H NMR (400 MHz, DMSO- d_6) δ 2.38 (s, 3H), 3.60 (s, 3H), 6.59 (d, J = 9.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 8.4, 1.6 Hz, 1H), 7.51 (brs, 1H), 7.83 (d, J = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 20.0 (CH₃), 28.9 (CH₃), 114.5 (CH), 120.0 (C), 121.0 (CH), 128.3 (CH), 130.9 (C), 131.8 (CH), 137.8 (C), 138.9 (CH), 161.0 (CO).

1,6-Dimethyl-3,5,7-trinitroquinolin-2(1H)-one (10): eluted with hexane/ethyl acetate = 8/2; yellow solid; mp 189–191 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 2.42 (s, 3H), 3.40 (s, 3H), 8.55 (s, 1H), 8.69 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 16.0 (CH₃), 35.3 (CH₃), 112.3 (C), 125.2 (C), 128.1 (CH), 132.8 (C), 132.8 (CH), 139.6 (C), 142.5 (C), 149.9 (C), 153.8 (CO); MS (EI, 70 eV) m/z = 308 (M⁺, 3), 220 (25), 191 (36), 115 (100), 105 (55); HRMS (EI) Calcd for C₁₁H₈N₄O₇ 308.0393, found 308.0393.

1,6-Dimethyl-5,7-dinitroquinolin-2(1H)-one (11): eluted with hexane/ethyl acetate = 7/3; yellow solid; mp 112–115 °C; ^1H NMR (400 MHz, DMSO- d_6) δ 2.37 (s, 3H), 3.33 (s, 3H), 6.92 (d, J = 10.0 Hz, 1H), 7.74 (d, J = 10.0 Hz, 1H), 8.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 15.6 (CH₃), 34.0 (CH₃), 114.6 (C), 123.2 (C), 125.3 (CH), 129.7 (CH), 131.8 (CH), 132.3 (C), 139.3 (C), 149.2 (C), 160.8 (CO); MS (EI, 70 eV) m/z = 263 (M⁺, 100), 233 (30), 173 (45); HRMS (EI) Calcd for C₁₁H₉N₃O₅ 263.0542, found 263.0542.

1,6-Dimethyl-3,5-dinitroquinolin-2(1*H*)-one (12): yellow needles; recrystallized from MeCN; mp 259–261 °C; ¹H NMR (400 MHz, CD₃CN) δ 2.44 (s, 3H), 3.77 (s, 3H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.81 (d, *J* = 9.2 Hz, 1H), 8.31 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 16.4 (CH₃), 30.9 (CH₃), 108.7 (C), 118.7 (CH), 124.8 (C), 128.3 (CH), 136.5 (CH), 139.2 (C), 142.1 (C), 148.2 (C), 152.9 (CO); MS (EI, 70 eV) *m/z* = 263 (M⁺, 38), 142 (41), 115 (57), 69 (100); HRMS (EI) Calcd for C₁₁H₉N₃O₅ 263.0542, found 263.0537.

1,8-Dimethylquinolin-2(1*H*)-one (14): yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.71 (s, 3H), 3.74 (s, 3H), 6.57 (d, *J* = 9.2 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.40 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.83 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 23.4 (CH₃), 35.6 (CH₃), 120.4 (CH), 121.8 (C), 122.3 (CH), 125.0 (C), 127.3 (CH), 135.1 (CH), 140.0 (CH), 140.7 (C), 163.1 (CO).

1,8-Dimethyl-3,6-dinitroquinolin-2(1*H*)-one (5): eluted with hexane/ethyl acetate = 7/3; yellow solid; mp 236–238 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.84 (s, 3H), 3.85 (s, 3H), 8.42 (d, *J* = 2.8 Hz, 1H), 8.80 (d, *J* = 2.8 Hz, 1H), 9.09 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 23.2 (CH₃), 37.0 (CH₃), 118.4 (C), 125.2 (CH), 128.4 (C), 131.1 (CH), 136.7 (CH), 140.3 (C), 142.0 (C), 146.0 (C), 155.4 (CO); MS (EI, 70 eV) *m/z* = 263 (M⁺, 95), 210 (58), 193 (53), 142 (80), 117 (100); HRMS (EI) Calcd for C₁₁H₉N₃O₅ 263.0542, found 263.0541.

1,8-Dimethyl-3,5,7-trinitroquinolin-2(1*H*)-one (15): eluted with hexane/ethyl acetate = 3/7; yellow solid; mp 188–190 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.85 (s, 3H), 3.82 (s, 3H), 8.53 (s, 1H), 8.60 (s, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 23.2 (CH₃), 37.7 (CH₃), 111.0 (C), 127.9 (CH), 131.3 (C), 131.6 (CH), 133.2 (C), 140.7 (C),

142.8 (C), 145.9 (C), 154.9 (CO); MS (EI, 70 eV) m/z = 308 (M^+ , 10), 130 (29), 101 (32), 75 (46), 69 (100); HRMS (EI) Calcd for $C_{11}H_8N_4O_7$ 308.0393, found 308.0395.

1,8-Dimethyl-3,5-dinitroquinolin-2(1*H*)-one (16): eluted with hexane/ethyl acetate = 3/7; yellow solid; mp 216–219 °C; 1H NMR (400 MHz, DMSO- d_6) δ 2.84 (s, 3H), 3.78 (s, 3H), 6.92 (d, J = 9.6 Hz, 1H), 7.66 (d, J = 9.6 Hz, 1H), 8.39 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 23.4 (CH₃), 36.4 (CH₃), 113.2 (C), 125.6 (CH), 129.5 (CH), 129.9 (C), 131.8 (C), 131.8 (CH), 140.0 (C), 146.0 (C), 162.1 (CO); MS (EI, 70 eV) m/z = 263 (M^+ , 100), 159 (28), 130 (20), 75 (17); HRMS (EI) Calcd for $C_{11}H_9N_3O_5$ 263.0542, found 263.0541.

(*Z*)-4-(2-Hydroxy-4-oxopent-2-en-3-yl)-1,8-dimethyl-6-nitroquinolin-2(1*H*)-one (21): orange solid; mp 192–194 °C; 1H NMR (400 MHz, CDCl₃) δ 1.90 (s, 6H), 2.85 (s, 3H), 3.89 (s, 3H), 6.75 (s, 1H), 8.24 (d, J = 2.4 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H), 16.86 (s, 1H); ^{13}C NMR (100 MHz, CDCl₃) δ 23.9 (2CH₃), 24.3 (CH₃), 37.1 (CH₃), 109.0 (C), 120.2 (CH), 122.8 (C), 125.9 (CH), 127.2 (C), 129.6 (CH), 142.3 (C), 146.0 (C), 146.4 (C), 164.0 (CO), 190.7 (CO); MS (EI, 70 eV) m/z = 316 (M^+ , 100), 263 (75); HRMS (EI) Calcd for $C_{16}H_{16}N_2O_5$ 316.1059, found 316.1062.

1-Methyl-6,8-dinitro-2-oxo-1,2-dihydroquinoline-4-carbonitrile (23): yellow powder; mp 168–171 °C; IR (KBr) 2247 cm⁻¹; 1H NMR (400 MHz, DMSO- d_6) δ 3.37 (s, 3H), 7.89 (s, 1H), 8.70 (d, J = 2.6 Hz, 1H), 9.07 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 34.8 (CH₃), 113.6 (CN), 119.4 (C), 121.7 (C), 123.6 (CH), 124.7 (CH), 132.3 (CH), 137.2 (C), 138.7 (C), 140.5 (C), 160.1 (CO); MS (EI, 70 eV) m/z = 274 (M^+ , 68), 244 (100), 182 (63), 127 (61); HRMS (EI) Calcd for $C_{11}H_6N_4O_5$ 274.0338, found 274.0337.

1,1'-Dimethyl-6,6',8,8'-tetranitro-2,2'-dioxo-1,1',2,2'-tetrahydro-3,4'-biquinoline-4-carbonitrile (24): reddish brown oil; IR (KBr) 2240 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 3.45 (s, 3H), 3.46 (s, 3H), 7.30 (s, 1H), 8.78 (d, $J = 2.4$ Hz, 1H), 8.82 (d, $J = 2.4$ Hz, 1H), 8.98 (d, $J = 2.4$ Hz, 1H), 9.20 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 34.9 (CH_3), 35.5 (CH_3), 112.8 (CN), 119.9 (C), 121.1 (C), 122.6 (C), 123.2 (CH), 124.1 (CH), 125.3 (CH), 125.8 (CH), 125.9 (CH), 136.9 (C), 137.4 (C), 137.5 (C), 138.7 (C), 138.9 (C), 140.7 (C), 140.8 (C), 142.7 (C), 159.6 (CO), 160.8 (CO); MS (EI, 70 eV) $m/z = 521$ (M^+ , 95), 491 (100); HRMS (EI) Calcd for $\text{C}_{21}\text{H}_{11}\text{N}_7\text{O}_{10}$ 521.0567, found 521.0560.

1,8-Dimethyl-5,7-dinitro-2-oxo-1,2-dihydroquinoline-4-carbonitrile (25): red solid; mp 221–223 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.78 (s, 3H), 3.69 (s, 3H), 7.86 (s, 1H), 8.50 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 23.2 (CH_3), 38.1 (CH_3), 108.3 (CN), 112.0 (C), 115.6 (C), 130.7 (CH), 131.0 (C), 133.6 (C), 136.4 (CH), 138.3 (C), 146.8 (C), 160.1 (CO); MS (EI, 70 eV) $m/z = 288$ (M^+ , 40), 184 (100); HRMS (EI) Calcd for $\text{C}_{12}\text{H}_8\text{N}_4\text{O}_5$ 288.0495, found 288.0494.

1,8-Dimethyl-5-nitro-2-oxo-1,2-dihydroquinoline-4-carbonitrile (26): yellow solid; mp 215–217 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.86 (s, 3H), 3.77 (s, 3H), 7.02 (d, $J = 9.6$ Hz, 1H), 8.17 (d, $J = 9.6$ Hz, 1H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 23.7 (CH_3), 36.4 (CH_3), 113.4 (CN), 119.2 (C), 123.0 (C), 125.4 (CH), 129.2 (C), 129.7 (CH), 132.3 (C), 135.6 (CH), 145.1 (C), 162.3 (CO); MS (EI, 70 eV) $m/z = 243$ (M^+ , 53), 197 (62), 169 (100), 142 (67); HRMS (EI) Calcd for $\text{C}_{12}\text{H}_9\text{N}_3\text{O}_3$ 243.0644, found 243.0639.

1,8-Dimethyl-6-nitro-2-oxo-1,2-dihydroquinoline-4-carbonitrile (27): brown solid; mp 197–198 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 2.84 (s, 3H), 3.79 (s, 3H),

7.66 (s, 1H), 8.39 (d, $J = 2.4$ Hz, 1H), 8.41 (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 23.3 (CH₃), 36.8 (CH₃), 114.3 (CN), 117.8 (C), 119.4 (CH), 122.0 (C), 128.8 (C), 129.8 (CH), 130.7 (CH), 141.6 (C), 145.2 (C), 161.2 (CO); MS (EI, 70 eV) m/z = 243 (M⁺, 100), 228 (35), 169 (40); HRMS (EI) Calcd for C₁₂H₉N₃O₃ 243.0644, found 243.0637.

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Part B

One-step and Non-catalytic Intramolecular Redox Reactions of Conjugated all *E*-Dienals to Non-conjugated *Z*-Enoic Acids in Subcritical Water

Abstract

Superheated fluids as solvent were investigated in organic synthesis because of their special characteristics. Simple treatment of conjugated all *E*-dienals, (2*E*,4*E*)-hexa-2,4-dienal, in subcritical water afforded an intramolecular redox product, non-conjugated *Z*-enoic acid, (*Z*)-hex-3-enoic acid, in 42% yield without the usage of a metal catalyst in one-step under the conditions of 250 °C, 10 min, and 0.35 g/mL water amount. Similar treatment of the dienal in superheated benzyl alcohol produced non-conjugated *Z*-enoic ester benzyl (*Z*)-hex-3-enoate in 34% yield under the conditions of 300 °C, 30 min, and 0.5 g/mL benzyl alcohol amount. The obtained (*Z*)-hex-3-enoic acid was transformed to *cis*- β -hydroxy- γ -ethyl- γ -lactone in 90% yield by hydrogen peroxide at 60 °C for one day under solvent-free conditions.

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1. Introduction

1.1 Subcritical and supercritical water

Water is an ecological, environmental and safe substance widespread throughout nature. Ambient water at standard conditions (25 °C and 0.1 MPa) is an excellent solvent for many compounds because of its high dielectric constant, but it is poorly miscible with hydrocarbons and gases. Temperature and pressure have a great effect on the properties of water (Figure 1.1). At the critical point both phases become identical and the dividing meniscus disappears. The critical temperature (T_c), pressure (P_c), and density (ρ_c) are:¹ $T_c = 374\text{ °C}$, $P_c = 22.1\text{ MPa}$, $\rho_c = 0.32\text{ g/mL}$.

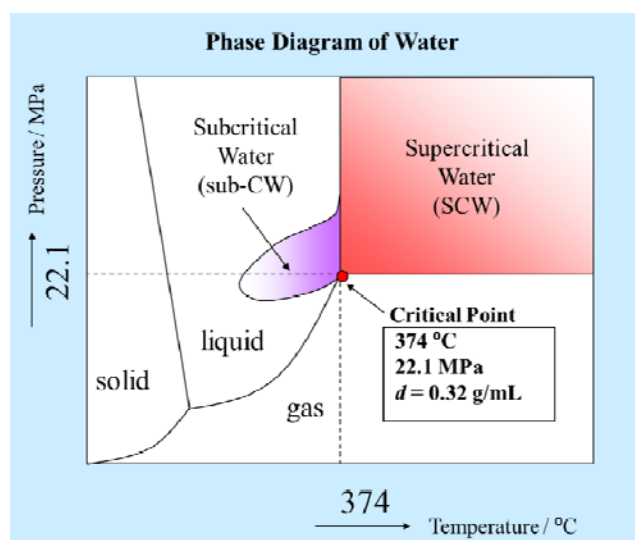


Figure 1.1 Properties of subcritical and supercritical water

In the supercritical state, various fluid properties change, including density of molecules, viscosity, dielectric constant, diffusion coefficient, and thermal conductivity. Because of supercritical water's intriguing properties, especially around the critical

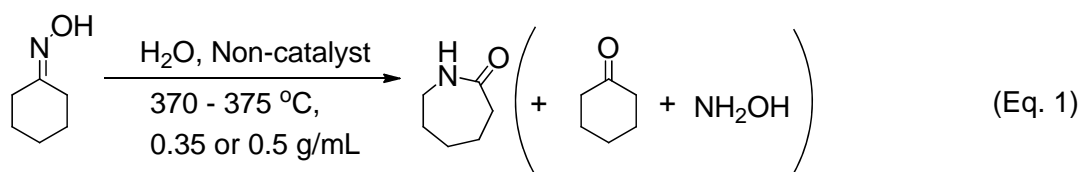
point, various studies have examined its characteristics. The dielectric constant of water at room temperature is 78 and decreases considerably with increasing temperature. Around the critical point of water, this value is nearly equal to the dielectric constant of polar organic solvents.² Therefore, subcritical water (sub-CW) and supercritical water (SCW) can form a homogeneous phase with inorganic and organic substances, and water itself works as an acid or base catalyst.³

In the early 1980s, the application of sub-CW and SCW as reaction media had been reported.⁴ For the last third decades, extensive applications of sub-CW and SCW as a reaction media were investigated, such as chemical reaction,⁵ materials synthesis,^{2,6} biomass processing,⁷ and waste treatment.⁸ Among these applications, sub-CW and SCW are in common use in chemical reactions as reaction systems.

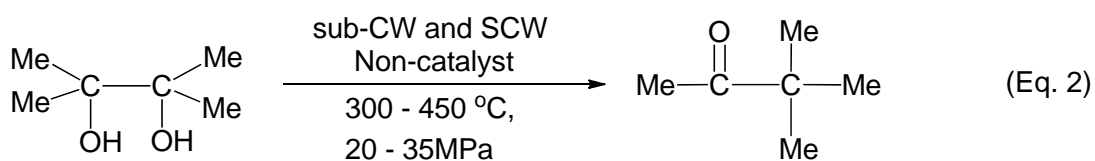
In contrast, much attention has been paid to superheated fluids such as sub-CW,⁹ SCW,⁹ and supercritical alcohols^{10,11} from the perspective of green reactions because of their unique properties. For example, extremely strong complexation effect under high pressure produces solvent clusters around the solute molecules, which leads to strong interactions between the solute and solvent molecules. In addition, a major characteristic of superheated fluids is that their inherent high temperatures cause vigorous vibration of the molecules in the system, which leads to high reactivity between them. By employing these remarkable properties, intriguing reactions were reported, such as the Beckmann rearrangement of cyclohexanone oxime (Eq. 1),¹² pinacol rearrangement of 2,3-dimethyl-2,3-butanediol (Eq. 2),¹³ and Cannizzaro reaction of formaldehyde (Eq. 3),¹⁴ acetaldehyde (Eq. 3),^{15,16} and benzaldehyde (Eq. 3)¹⁷ in SCW without any catalyst. Through the researches, we recently disclosed a series of unique reactions, such as non-catalytic green oxidation of alcohols in SCW without any

oxidant to give ketones and hydrogen gas (Eq. 4),¹⁸ highly selective non-catalytic Oppenauer oxidation of alcohols in SCW (Eq. 5),¹⁹ the first direct observation of radical species in sub-CW by means of ESR,²⁰ easy permethylation of catechols in SCW (Eq. 6),²¹ and effective aldol reactions in sub-CW (Eq. 7).²²

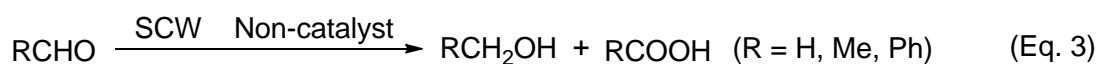
Beckmann rearrangement of cyclohexanone-oxime¹²



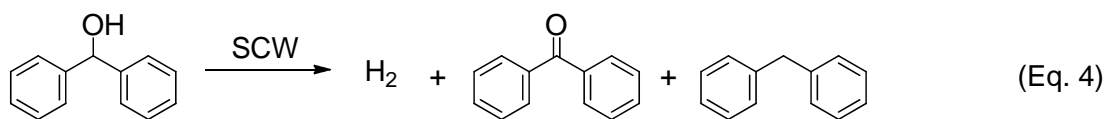
Pinacol rearrangement of 2,3-dimethyl-2,3-butanediol¹³



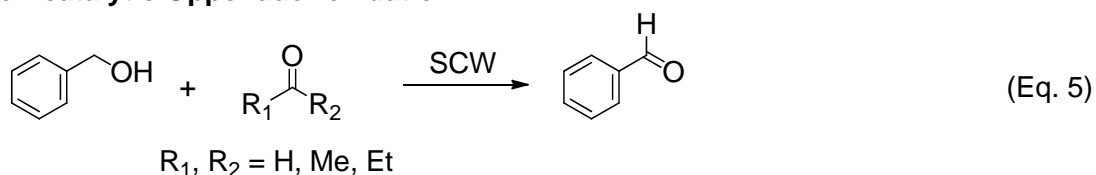
Cannizzaro reaction of aldehydes¹⁴⁻¹⁷



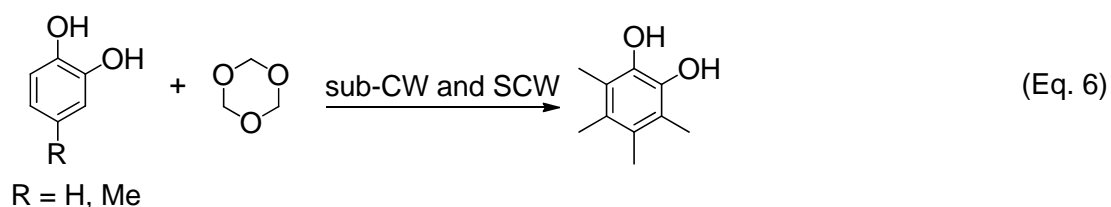
Non-catalytic green oxidation¹⁸



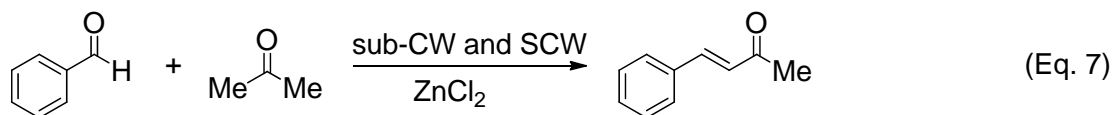
Non-catalytic Oppenauer oxidation¹⁹



Permethylation of catechols²¹



Cross-aldol reaction²²



1.2 Unsaturated acids and derivatives

Unsaturated acids and their derivatives are important substances to show various bioactivities. For example, naturally occurring unsaturated fatty acids, such as arachidonic, docosahexaenoic, and eicosapentaenoic acids, are quite important bio-precursors that lead to regulating reagents in bodies (Figure 1.2).^{23,24} Almost all naturally occurring fatty acids contain the *Z*-configuration in their double bonds, which is less stable than the *E*-configuration. In addition, simple (*Z*)-alk-3-enoic acids bearing one non-conjugated double bond are important in vivo, some of which are pheromones of certain coleopterous insects or intermediates used in their syntheses.²⁵⁻²⁷ Moreover, a brominated (*Z*)-alk-3-enoic acid derivative exhibits cytotoxicity against cultured cells;²⁸ 3-unsaturated amino acids are known to function as specific enzyme inhibitors and pyridoxal phosphate dependent enzymes;^{29,30} and an ester derivative is a potent odorant in Japanese Green Tea.³¹ Furthermore, (*Z*)-alk-3-enoic acid derivatives are the possible precursors of γ -lactones with alkyl chains exhibiting pheromone characteristics.³²

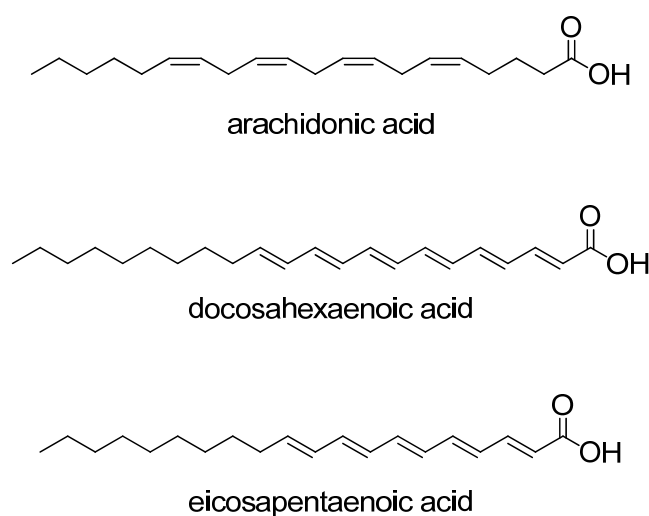
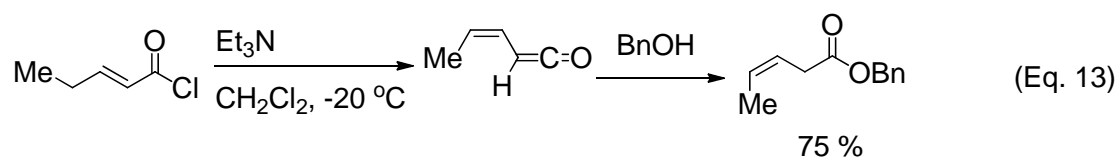
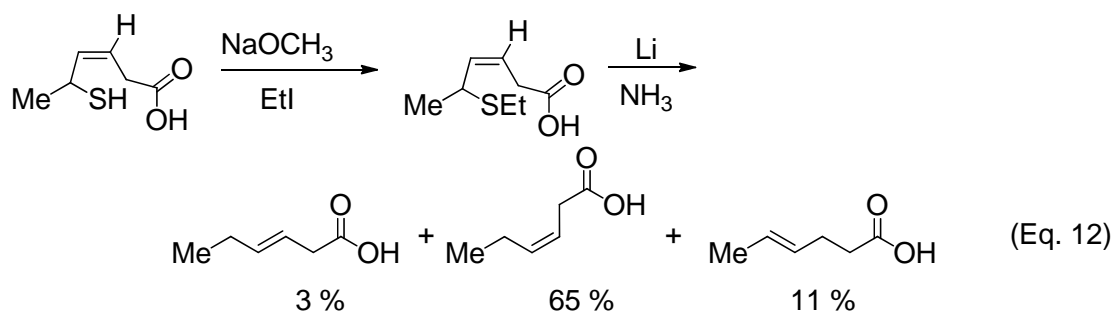
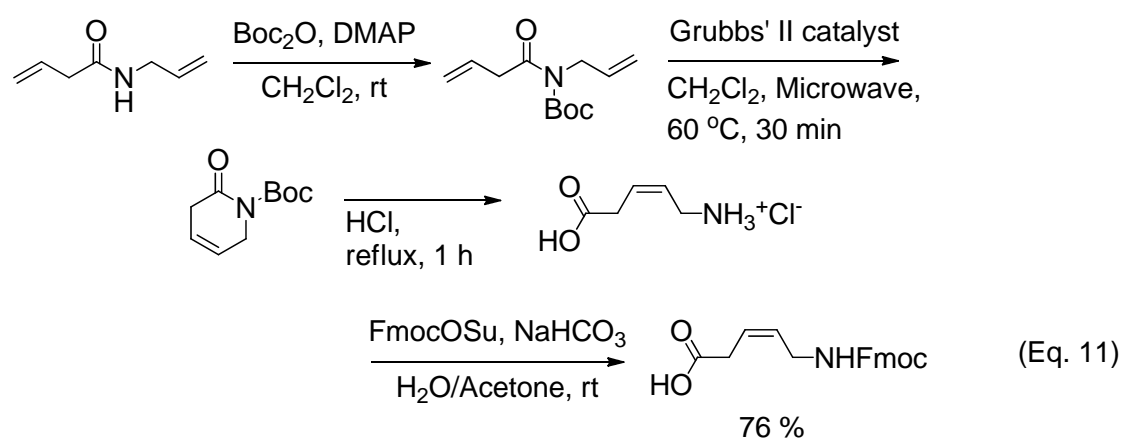
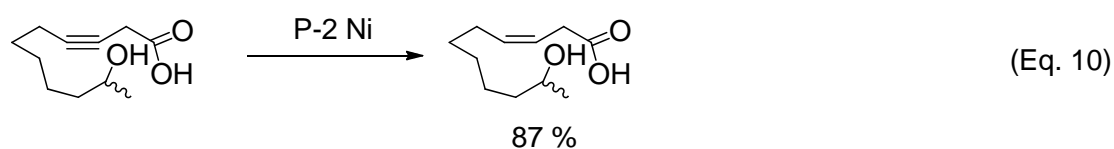
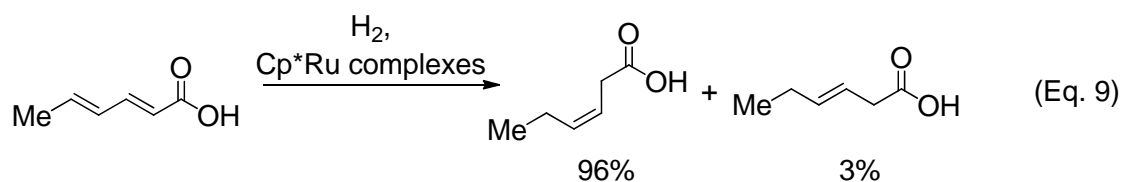
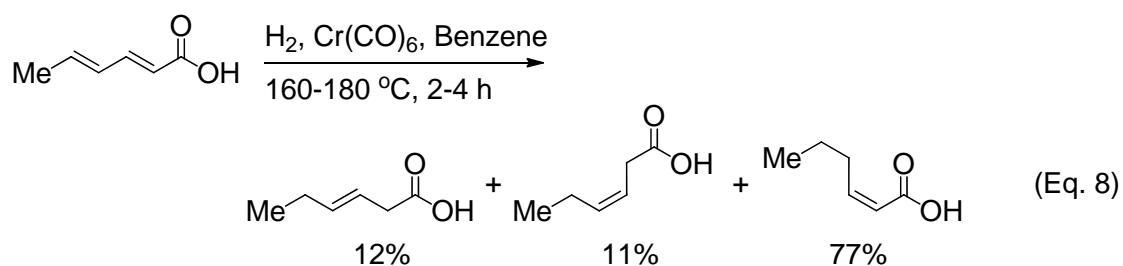


Figure 1.2 Unsaturated fatty acids

Intense research to obtain thermodynamically less-stable *Z* isomers of non-conjugated unsaturated hexenoic acids and their related compounds has led to several methods for selective hydrogenation using transition metal complexes. Hydrogenation of sorbic acid catalyzed by $\text{Cr}(\text{CO})_6$ ³³ or $[\text{Cp}^*\text{Ru}]^+$,^{34,35} which fixes two double bonds of sorbic acid to *s-cis* conformation in the metal center, is a typical method (Eq. 8 and 9). The classical P-2 Ni catalyst is also available through the hydrogenation of unsaturated acid bearing a triple bond (Eq. 10).^{26,27} Olefin metathesis using the Grubbs' II catalyst is employed to afford cyclic derivatives containing a double bond with the *Z*-configuration followed by ring cleavage (Eq. 11).³⁶ Lithium–ammonia reduction of 2-thiophenecarboxylic acid (Eq. 12)³⁷ and the addition of alcohol to ketene intermediate from corresponding acid chloride in situ (Eq. 13)³⁸ also appeared in the literature.



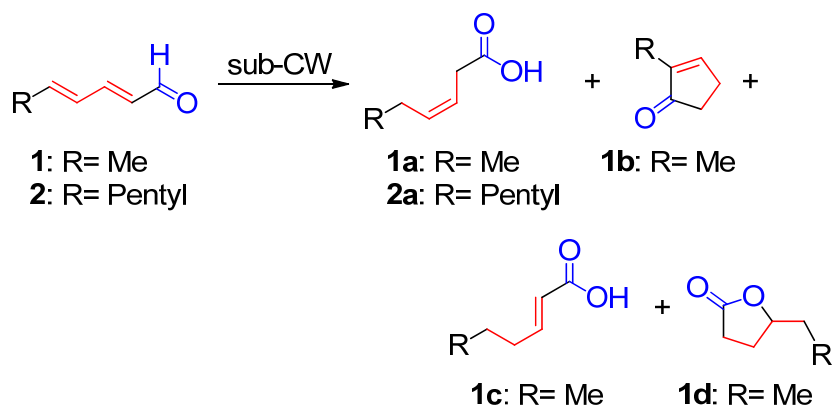
1.3 Research purpose

In this thesis, we tried to delineate the organic transformations of conjugated dienals into non-conjugated unsaturated acids with *Z*-form by thermal intramolecular rearrangement in superheated fluids. An example of metal-free, non-catalytic, and simple preparation of (*Z*)-alk-3-enoic acid from (*2E,4E*)-alka-2,4-dienal in sub-CW will be studied.

2. Results and Discussion

2.1 Reaction of *2E,4E*-dienals in subcritical water

(*2E,4E*)-Hexa-2,4-dienal (**1**) was treated in sub-CW under different conditions of reaction temperature, reaction time, and water amount (Scheme 2.1 and Table 2.1). When the reaction was performed at a low temperature (200 °C), only a small amount of **1a** with a trace amount of **1b** were obtained (entry 1). The yield of **1a** increased with temperature up to 250 °C, while a higher temperature (350 °C) did not yield the product (entries 1, 5, 8, and 9). These results indicate that the reaction has high activation energy and that the products are not stable at high temperatures. While microwave heating was used instead of molten salt bath, yield of **1a** increased to 37%, with small amount of **1b** (entry 2). It is also noteworthy that no product was produced in the absence of water (entry 3), indicating water plays a critical role in the reaction. In addition, water amount dependence was observed for the formation of **1a** (entries 3-6) at the fixed temperature (250 °C) and in fixed reaction time (10 min), suggesting solubility of **1** to water is improved till 0.35 g/mL water amount.



Scheme 2.1 Reactions of (*2E,4E*)-hexa-2,4-dienal (**1**) and (*2E,4E*)-deca-2,4-dienal (**2**) in sub-CW

stability, (*E*)-hex-2-enoic acid (**1c**),³⁹ and γ -ethyl- γ -lactone (**1d**),⁴⁰ which should be derived from the cyclization of **1a** or **1c** under the reaction conditions (entry 7).

For intermolecular redox reactions of aldehydes, the conventional Cannizzaro reaction is well known to simultaneously give a reduction product of alcohol and an oxidation product of acid under strongly basic conditions. However, when the Cannizzaro reaction is performed under sub-CW and SCW conditions, the reaction proceeds even without a catalyst.¹⁴⁻¹⁷ For intramolecular redox reaction of conjugated enals, unique catalytic intramolecular redox reactions of enals affording saturated acids as well as lactones were reported.⁴¹ However, our reaction is, to the best of our knowledge, the first example of non-catalytic intramolecular Cannizzaro reaction of dienals affording non-conjugated unsaturated acids **1a**.

When the present reaction was applied to (*2E,4E*)-deca-2,4-dienal (**2**) with a long alkyl chain under similar reaction conditions of 250 °C, 30 min, and 0.35 g/mL water amount, corresponding (*Z*)-dec-3-enoic acid (**2a**), which is a precursor of a γ -lactone derivative exhibiting pheromone character,³³ was nicely obtained in 20% yield.

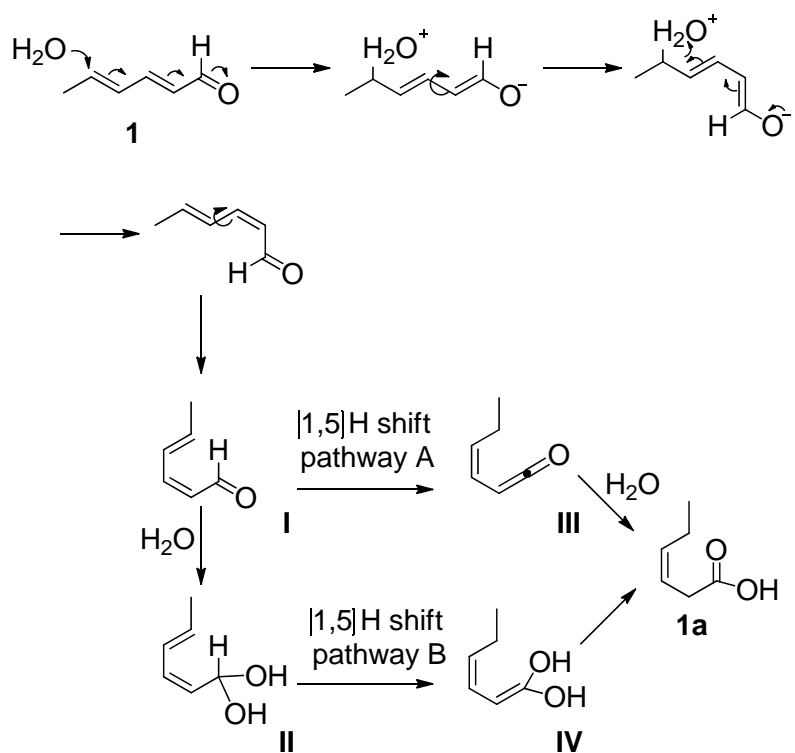
2.2 Plausible reaction mechanism

2.2.1 Plausible reaction mechanism for the formation of (Z)-hex-3-enoic acid

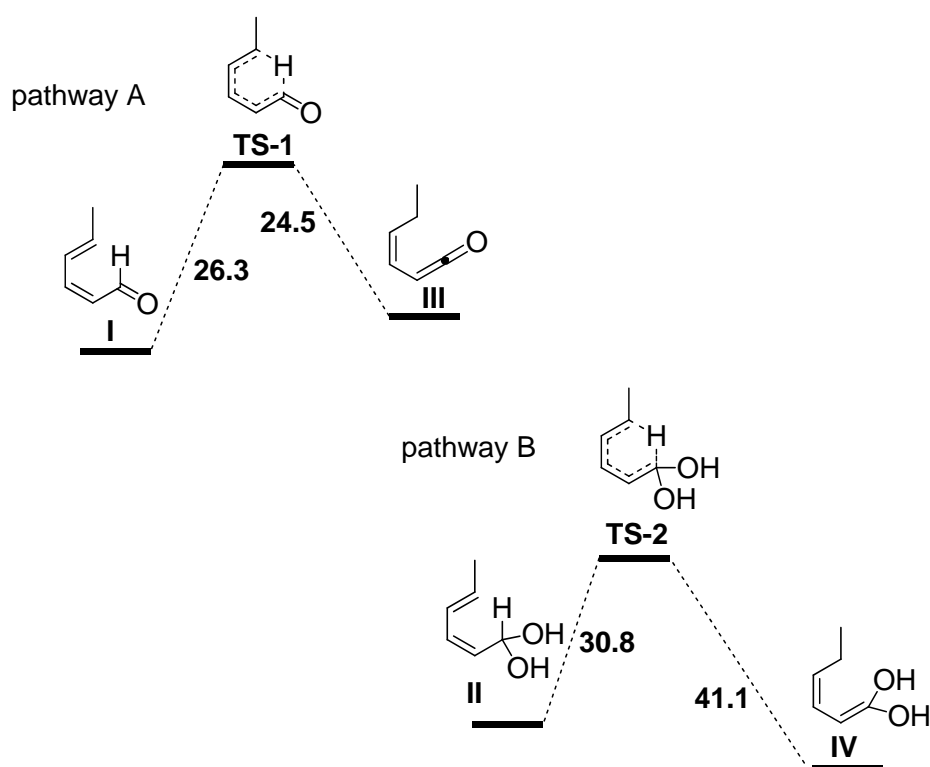
As plausible reaction pathways, we propose two possibilities via ketene intermediate (pathway A) and *gem*-diol intermediate (pathway B), both of which include [1,5]hydrogen shift as the key step (Scheme 2.2). Thermal reactions yielding Z-configuration of double bonds employ [1,5]hydrogen shift as a well-established methodology. Interesting applications of [1,5]hydrogen shift recently appeared as a key process for the activation of C-H bonds, although the reactions required acid catalysts.^{42,43} Intermediate **I** can be produced via Michael addition of water followed by the *E/Z* isomerization of a double bond and dehydration. Further hydration of intermediate **I** would afford *gem*-diol intermediate **II** (Scheme 2.2).

Theoretical considerations by DFT calculations suggested a plausible reaction pathway via [1,5]hydrogen shift leading to a ketene intermediate **III** (Scheme 2.3). The activation energy from the intermediate **I** to the transition state **TS-1** is calculated to be 26.3 kcal/mol. Once the ketene intermediate **III** is generated, water can be easily added to produce carboxylic acid **1a**. As an additional possibility, we supposed the reaction pathway via *gem*-diol intermediate **II** because aldehyde intermediate **I** can be easily hydrated in high-pressure water to produce intermediate **II** (Scheme 2.2).

Similar DFT calculation indicates that the pathway leading to the transition state **TS-2** from the *gem*-diol intermediate **II** requires slightly higher activation energy of 30.8 kcal/mol (Scheme 2.3). The resulting intermediate **IV** would get tautomerism to produce non-conjugated acid **1a**.



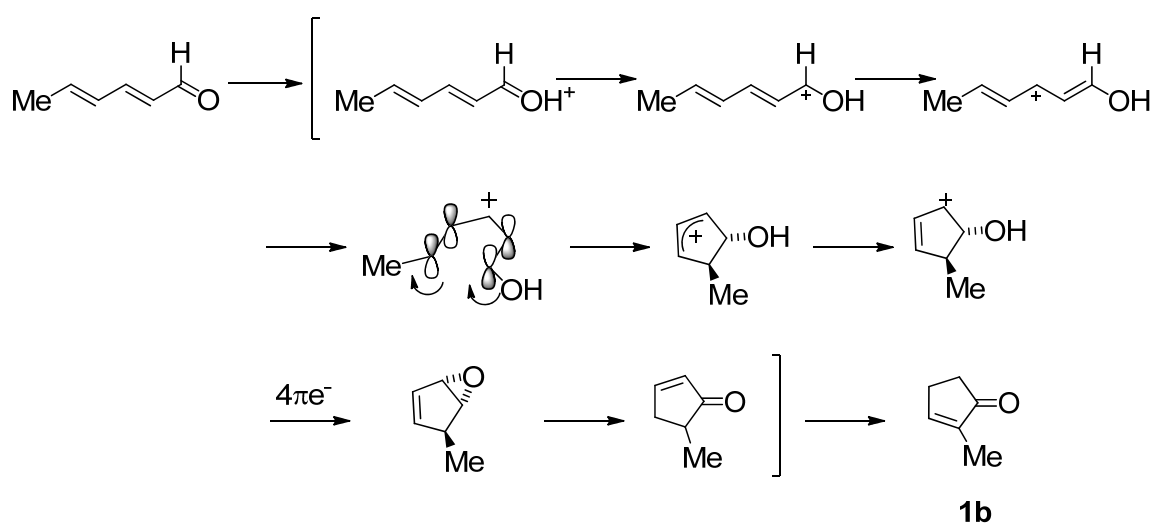
Scheme 2.2 Plausible reaction pathways from **1** to **1a**



Scheme 2.3 Activation energies of the reactions via a ketene intermediate (pathway A) and a *gem*-diol intermediate (pathway B) (Numbers are relative energies in kcal/mol calculated by DFT B3LYP/6-31G* plus zero-point vibrational energy)

2.2.2 Plausible reaction mechanism for the formation of 2-methycyclopent-2-enone

Concerning the formation of cyclopentenones, Miller *et al.* reported the reaction of dienal derivatives via Nazarov-type cyclization or hetero $[\pi 4a+\pi 2a]$ concerted bond formation (Scheme 2.4).⁴⁴ However, the critical differences between their and our reactions are the configuration of double bonds in the reactants and the use of catalysts. The researchers specifically used 2*Z*,4*E*-isomer as a substrate in dichloromethane in the presence of strong Lewis acids as catalysts, while we used 2*E*,4*E*-isomer and only water without any catalyst. Similar cyclization was reported for the congested dienal with plural sterically bulky groups via a ketene intermediate as a special case;⁴⁵ however, non-substituted simple dienal **1** was used in our reaction.

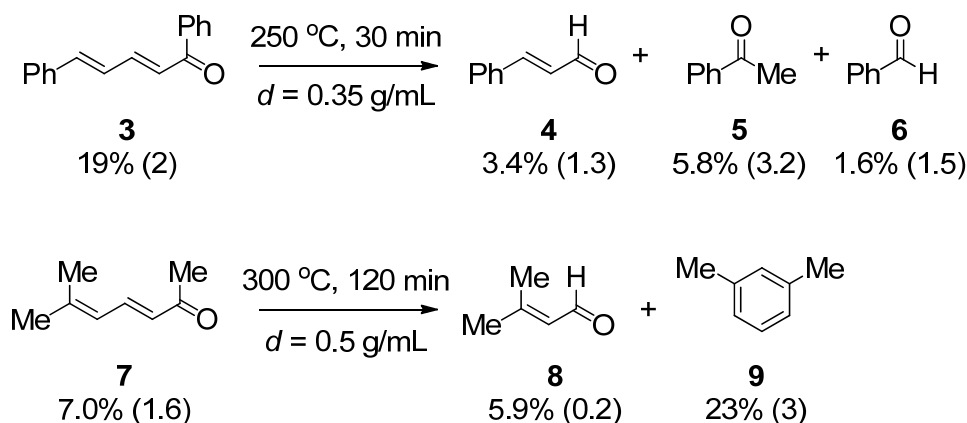


Scheme 2.4 Nazarov-type cyclization for the formation of **1b**

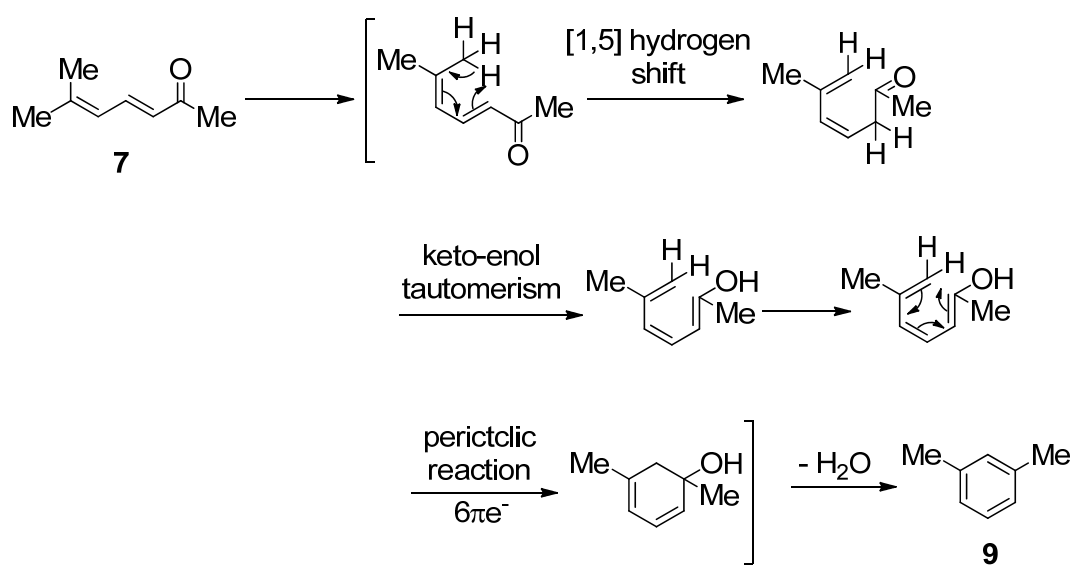
2.3 Reaction of 2*E*,4*E*-ketones in subcritical water

For conjugated ketone derivatives such as (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**3**) and (3*E*,5*E*)-6-methylhepta-3,5-dien-2-one (**7**), however, a remarkable difference in reaction behavior was observed to continuously produce retro-aldol products.

When (2*E*,4*E*)-1,5-diphenylpenta-2,4-dien-1-one (**3**) was treated with 3.5 mL H₂O under 250 °C for 30 min, the yield of cinnamaldehyde (**4**), acetophenone (**5**), benzaldehyde (**6**) were 3.4%, 5.8%, 1.6%, respectively, with the recovery of **3** was 19%. Furthermore, when (3*E*,5*E*)-6-methylhepta-3,5-dien-2-one (**7**) was treated with 5 mL H₂O under 300 °C for 120 min, 3-methylbut-2-enal (**8**) in addition to a cyclization product, *m*-xylene (**9**) were obtained with 5.9%, 23% yield, respectively (Scheme 2.5). Judging from these results, the aldehyde group is indispensable for the intramolecular redox reactions and the cyclization. The formation of **9** can be explained by thermal electrocyclic reaction of a 6 π electron system of enol generated by tautomerism of **7** followed by dehydration (Scheme 2.6).^{46,47}



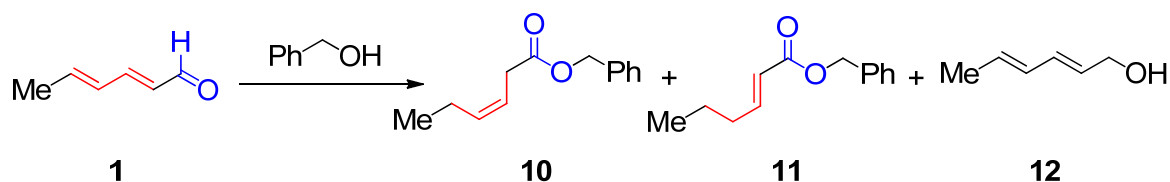
Scheme 2.5 Reaction of dienones in sub-CW



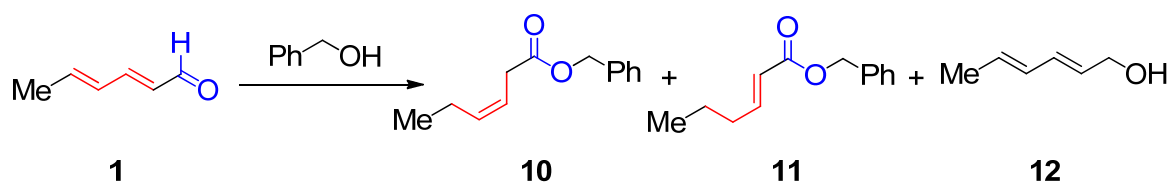
Scheme 2.6 Thermal electrocyclic reaction for the formation of compound **9**

2.4 Reaction of (2*E*,4*E*)-hexa-2,4-dienal in superheated benzyl alcohol

According to the reaction pathway proposed in Scheme 3, the reaction in superheated alcohol instead of sub-CW should afford a corresponding ester instead of the acid. The reaction of **1** in high-temperature benzyl alcohol (300 °C, 30 min, and 0.2 g/mL alcohol amount) actually yielded corresponding ester, benzyl (*Z*)-hex-3-enoate (**10**),³⁸ in 31% yield as expected, concomitant with benzyl (*E*)-hex-2-enoate (**11**)⁴⁸ in 4% and (2*E*,4*E*)-hexa-2,4-dienol (**12**) in 5% yield (Scheme 2.7 and Table 2.2). Alcohol **12** should be produced by Meerwein–Ponndorf–Verley (MPV) reduction of aldehyde **1** in the presence of a large excess amount of benzyl alcohol because the reaction conditions were the variant of representative non-catalytic MPV reduction.¹¹ Thus, it is truly noteworthy that the ester was obtained as a main product from aldehyde directly even though under MPV reduction conditions.



Scheme 2.7 Reaction of (2*E*,4*E*)-hexa-2,4-dienal (**1**) in superheated benzyl alcohol

Table 2.2 Reaction of **1** in superheated benzyl alcohol^a

Entry	Alcohol amount/g/mL ^b	Time/min	Yield (%)		Recovery of 1 /%
			10	12	
1 ^c	0.15	30	2 (0.2)	80 (4)	—
2 ^d	0.15	30	18 (1)	25 (7)	—
3	0.15	30	32 (0.3)	—	4 (0.1)
4	0.2	30	31 (2)	—	5 (1)
5	0.3	30	31 (4)	—	8 (2)
6	0.4	30	32 (1)	—	9 (1)
7	0.5	30	34 (1)	—	13 (0.5)

^a100 mg (1.04 mmol) of **1** was reacted at 300 °C, Mean value is given for a minimum of three runs, Standard deviation is shown in parentheses;

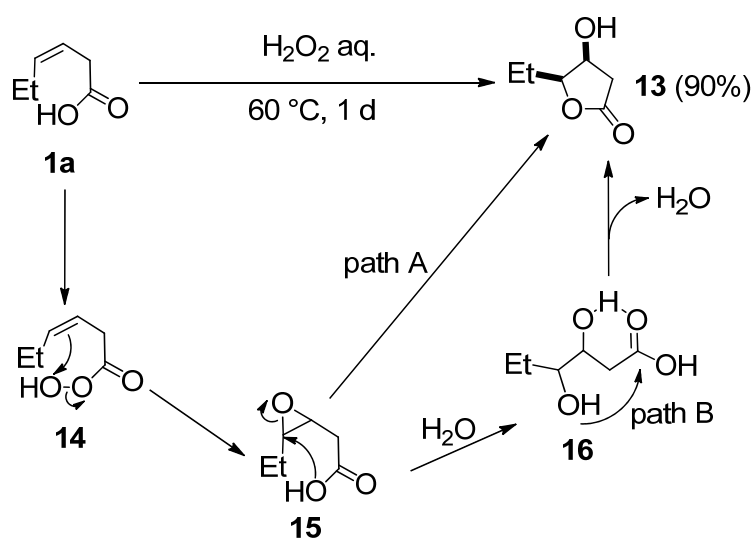
^bAlcohol amount was defined as the weight of benzyl alcohol (g)/reactor volume (mL);

^cReaction temperature at 200 °C;

^dReaction temperature at 250 °C.

2.5 Reaction of (Z)-hex-3-enoic acid with hydrogen peroxide

The bifunctionality of the unsaturated acid prompted us to further study chemical transformation. A C=C bond of an alkene is generally oxidized by peracid such as *m*CPBA or by a combination of hydrogen peroxide and acid. Thus, intramolecular oxidation appears to be possible when unsaturated acids are treated with hydrogen peroxide under solvent-free conditions; however, oleic acid, a typical unsaturated acid, is intact upon heating with hydrogen peroxide at 60 °C. In contrast, β,γ -unsaturated acid **1a** efficiently reacted under the same conditions to afford *cis*- β -hydroxy- γ -ethyl- γ -lactone (**13**)⁴⁹ in 90% yield (Scheme 2.8). It is considered that intramolecular oxidation readily proceeds, leading to epoxide **15** when **1a** is converted to peracid **14** by hydrogen peroxide. The successive ring expansion is caused by participation of the carboxyl group to form a lactone framework (path a), although an additional pathway via diol **16** is possible (path b). This reaction does not require a solvent or a reagent other than hydrogen peroxide and furnishes *cis*- γ -lactone **13** as a single isomer, which is promising for application to organic syntheses.



Scheme 2.8 Tandem intramolecular oxidation-ring expansion affording *cis*- γ -lactone **13**

3. Conclusions

The organic one-step transformation of conjugated dienals into non-conjugated unsaturated acid derivatives was achieved in superheated fluids. It is of importance that thermodynamically less-stable *Z* isomers of unsaturated acid derivatives were produced mainly by simple treatment of all *E*-dienals in superheated fluids. In addition, the obtained non-conjugated unsaturated acid was converted to the biologically active γ -lactone with a hydroxyl group by hydrogen peroxide in one step.

4. Experimental Section

4.1 General information

(2*E*,4*E*)-Hexa-2,4-dienal (**1**) and (2*E*,4*E*)-hexa-2,4-dienol (**12**) were purchased from Alfa Aesar. Cinnamaldehyde (**4**), acetophenone (**5**), benzaldehyde (**6**), 3-methylbut-2-enal (**8**), *m*-xylene (**9**), 2,4-dinitrophenylhydrazine, and benzyl alcohol were purchased from Nacalai Tesque Inc. (2*E*,4*E*)-1,5-Diphenylpenta-2,4-dien-1-one (**3**), (3*E*,5*E*)-6-methylhepta-3,5-dien-2-one (**7**) and silica gel (Wakogel C-200) were purchased from Wako Pure Chemical Industries Co. Ltd. (2*E*,4*E*)-Deca-2,4-dienal (**2**), *n*-decane, *n*-dodecane, and *n*-tridecane were obtained from Tokyo Chemical Industry Co. Ltd. They were used as received without further purification. NMR spectra were obtained using Varian UNITY INOVA spectrometer and Bruker AVANCE III 400N (400 MHz). GC-MS analyses were performed on a Shimadzu QP5050 with DB-1 column. GC analyses were performed on a Shimadzu GC-17A and DB-1 or CBP-5 column. Recoveries of reactants (percentage of reactant recovered to that loaded in the reaction) and yields of products were determined by internal standard methods on GC. *n*-Decane, *n*-dodecane, and *n*-tridecane were used as the internal standards. Products were identified by comparing the ¹H NMR and/or GC-MS spectra with those of authentic samples. Microwave heating was performed using Anton Paar Monowave 300 microwave Synthesis Reactor.

4.2 General procedure for reactions in subcritical water

(2*E*,4*E*)-hexa-2,4-dienal (**1**) and reverse osmosis water, in which the dissolved oxygen was removed by N₂ gas bubbling for 30 min, were introduced into an SUS 316 batch-type reactor (10 mL volume). To remove the oxygen in the reactor, the reactor was purged with N₂ for 10 min and sealed with a screw cap, which was equipped with a thermocouple for measuring the inner reactor temperature. The reactor was then placed in a molten salt bath, which was maintained at an appropriate temperature and heated for an appropriate time. A period of approximately 20-30 s was required to raise the inner temperature of the reactor to 200-350 °C. The reaction was quenched by placing the reactor into an ice-water bath. The screw cap was opened after the reactor cooled completely. Microwave heating was done in a glass reaction vessel. A period of approximately 3.5 min was required to raise the temperature of the reactor to 220 °C and approximately 4.5 min was required to cool the temperature to 60 °C. The reaction mixture was extracted with ethyl ether three times. The organic phase was separated from the water phase, and the solvent was evaporated in vacuo to produce crude products. These crude products were purified by using silica gel chromatography (Wako C-200, ether and hexane) and GPC (JAI gel 1H and 2H, chloroform) when necessary.

4.3 Reaction of (Z)-hex-3-enoic acid (**1a**) with hydrogen peroxide

A mixture of 34 mg (0.30 mmol) of (Z)-hex-3-enoic acid (**1a**) and 150 μ L of 30% H₂O₂ solution (1.47 mmol) was heated at 60 °C for 1 day with vigorous stirring. The solvent was removed under reduced pressure to afford 35.4 mg (0.27 mmol, 90%) of *cis*- β -hydroxy- γ -ethyl- γ -lactone as a single product.

4.4 Characterization data for products

(Z)-Hex-3-enoic acid (1a): ^1H NMR (400 MHz, CDCl_3) δ 5.62 (dt, $J = 10.8, 7.1, 1.4$ Hz, 1H), 5.51 (dt, $J = 10.8, 7.1, 1.4$ Hz, 1H), 3.14 (dd, $J = 7.1, 1.4$ Hz, 2H), 2.06 (qdd, $J = 7.6, 7.1, 1.4$ Hz, 2H), 0.98 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.4, 135.7, 119.4, 32.4, 20.7, 13.8; MS (EI) m/z : 114 [M^+].

2-Methycyclopent-2-enone (1b): the structure of **1b** was determined as 2,4-dinitrophenylhydrazone derivative **17**.⁵⁰ To a mixture of 800 mg of moist 2,4-dinitrophenylhydrazine (50% water, ca. 21 mmol), 2 mL conc. H_2SO_4 , 3 mL water, and 10 mL ethanol was added a solution of the crude products **1b** in 20 mL ethanol. The resulting precipitate was filtered. The filtrate was washed with water (30 mL \times 3) and dried in vacuo to afford 408 mg of solids, which were chromatographed on silica gel (CH_2Cl_2 /hexane) to give 46.3 mg of **17** as a red solid: mp 201–202 °C from CH_2Cl_2 /hexane; ^1H NMR (400 MHz, CDCl_3) δ 10.90 (s, 1H), 9.15 (d, $J = 2.6$ Hz, 1H), 8.31 (dd, $J = 9.6, 2.6$ Hz, 1H), 8.00 (d, $J = 9.6$ Hz, 1H), 6.55–6.52 (m, 1H), 2.75–2.65 (m, 4H), 1.96 (td, $J = 1.9, 1.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 144.7, 139.2, 129.9, 123.7, 116.4, 29.2, 26.0, 11.6; HRMS (EI) m/z 276.0858 [M^+] calculated for $\text{C}_{12}\text{H}_{12}\text{N}_4\text{O}_4$: 276.0859.

(E)-Hex-2-enoic acid (1c): ^1H NMR (400 MHz, CDCl_3) δ 7.08 (dt, $J = 16.0, 7.2$ Hz, 1H), 5.83 (dt, $J = 16.0, 1.6$ Hz, 1H), 2.21 (tdd, $J = 7.2, 7.2, 1.6$ Hz, 2H), 1.51 (qt, $J = 7.2, 7.2$ Hz, 2H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.6, 152.2, 120.6, 34.3, 21.1, 13.6; MS (EI) m/z : 114 [M^+].

γ -Ethyl- γ -lactone (1d): ^1H NMR (400 MHz, CDCl_3) δ 4.48–4.40 (m, 1H), 2.54 (dd, $J = 7.2, 2.0$ Hz, 2H), 2.37–2.27 (m, 1H), 1.92–1.59 (m, 3H), 1.01 (t, $J = 7.2$ Hz, 3H); ^{13}C

NMR (100 MHz, CDCl₃) δ 177.3, 82.2, 28.8, 28.5, 27.4, 9.4; MS (EI) m/z : 114 [M⁺].

(E)-Hex-2-enoic acid (2a): the structure of **2a** was determined leading to methyl ester **18**.³³ An ether solution of a crude **2a** in sub-CW was treated by an excess amount of diazomethane in ether at room temperature. Usual work up followed by silica gel chromatography (ether/hexane) and GPC (JAI gel 1H+2H, CHCl₃) afforded **18** as an oil. ¹H NMR (400 MHz, CDCl₃) δ 5.59 (dtt, J = 9.4, 5.2, 0.8 Hz, 1H), 5.56 (dtt, J = 9.4, 5.2, 0.8 Hz, 1H), 3.68 (s, 3H), 3.09 (dd, J = 5.2, 0.8 Hz, 2H), 2.03 (tdd, J = 6.8, 5.2, 0.8 Hz, 2H), 1.40–1.21 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.5, 133.6, 120.6, 51.8, 32.8, 31.7, 29.3, 28.9, 27.4, 22.6, 14.0; MS (EI) m/z : 184 [M⁺].

Benzyl (Z)-hex-3-enoate (10): ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.30 (m, 5H), 5.59 (dtt, J = 10.8, 6.1, 0.8 Hz, 1H), 5.54 (dtt, J = 10.8, 6.1, 0.8 Hz, 1H), 5.13 (s, 2H), 3.14 (dd, J = 6.1, 0.8 Hz, 2H), 2.10–2.01 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.8, 136.0, 135.3, 128.5, 128.2, 128.1, 120.0, 66.4, 32.9, 20.7, 13.9; MS (EI) m/z : 204 [M⁺].

Benzyl (E)-hex-2-enoate (11): ¹H NMR (400 MHz, CDCl₃) δ 7.40–7.29 (m, 5H), 7.02 (dt, J = 15.6, 7.0 Hz, 1H), 5.87 (dt, J = 15.6, 1.6 Hz, 1H), 5.18 (s, 2H), 2.18 (tdd, J = 7.2, 7.0, 1.6 Hz, 2H), 1.49 (qt, J = 7.4, 7.2 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.5, 149.8, 136.3, 128.5, 128.1, 128.1, 121.1, 66.0, 34.2, 21.2, 13.6; MS (EI) m/z : 204 [M⁺].

cis- β -Hydroxy- γ -ethyl- γ -lactone (13): a mixture of 34 mg (0.30 mmol) of **1a** and 150 μ L of 30% H₂O₂ solution (1.47 mmol) was heated at 60 °C for 1 day with vigorous stirring. The solvent was removed under reduced pressure to afford 35.4 mg (0.27 mmol, 90%) of *cis*- β -hydroxy- γ -ethyl- γ -lactone (**13**) as a single product. The relative configuration of **13** was determined by comparison of the coupling constants between

the α -methylene and the β -methyne groups with those of the authentic samples, *cis*- and *trans*- β -hydroxy- γ -methyl- γ -lactones.⁵¹ Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.50 (ddd, $J = 5.5, 3.6, 0.9$ Hz, 1H), 4.31 (ddd, $J = 7.8, 6.3, 3.6$ Hz, 1H), 2.81 (dd, $J = 18.0, 5.5$ Hz, 1H), 2.57 (dd, $J = 18.0, 0.9$ Hz, 1H), 1.96–1.70 (m, 2H), 1.06 (dd, $J = 7.4, 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.6, 86.7, 68.7, 39.5, 21.5, 9.8; MS (EI) m/z : 102 [$\text{M}^+ - \text{CO}$].

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List of Publications and Presentations

Publications

1. **One-step and non-catalytic intramolecular redox reactions of conjugated all *E*-dienals to non-conjugated *Z*-enoic acids in subcritical water**

Xin Chen, Kana Sumoto, Sotatsu Mitani, Tetsuya Yamagami, Kazuya Yokoyama, Pengyu Wang, Shotaro Hirao, Nagatoshi Nishiwaki, Kazuya Kobiro, *The Journal of Supercritical Fluids* **2012**, 62, 178-183.

2. **Reactive 2-quinolones dearomatized by steric repulsion between 1-methyl and 8-substituted groups**

Xin Chen, Kazuya Kobiro, Haruyasu Asahara, Kiyomi Kakiuchi, Ryuichi Sugimoto, Kazuhiko Saigo, Nagatoshi Nishiwaki, *Tetrahedron* **2013**, 69, 4624-4630.

Presentations

- 1. Synthesis of unsaturated fatty acids in subcritical water via intramolecular redox reaction**

Xin Chen, Kana Sumoto, Sotatsu Mitani, Pengyu Wang, and Kazuya Kobiro

第 27 回若手化学者のための化学道場, 9 月, **2011**, 高知.

- 2. A new reaction of dienals initiated by addition of alcohols under high-temperature and high-pressure conditions**

Xin Chen, Kana Sumoto, Sotatsu Mitani, Pengyu Wang, and Kazuya Kobiro

日本化学会第 91 春季年会, 3 月, **2011**, 東京.

- 3. One-step, non-catalytic intramolecular redox reactions of conjugated all *E*-dienals to non-conjugated *Z*-enoic acids in subcritical water**

Xin Chen, Kana Sumoto, and Kazuya Kobiro

The Seventh International Symposium on Integrated Synthesis, October, **2011**, Kobe.

- 4. Functionalization of 1-methyl-2-quinolone framework induced by cyanide addition**

Xin Chen, Kazuya Kobiro, Ryuichi Sugimoto, Kazuhiko Saigo, and Nagatoshi Nishiwaki

第 42 回複素環化学討論会, 10 月, **2012**, 京都.

5. Studies on the reactivity of trinitroquinolone and functionalization

Xin Chen, Kazuya Kobi-ro, Ryuichi Sugimoto, Kazuhiko Saigo, and Nagatoshi Nishiwaki

日本化学会第 93 春季年会, 3 月, **2013**, 滋賀.

6. Activation of 1-methyl-2-quinolone framework using steric repulsion between substituents

Haruyasu Asahara, Xin Chen, Kazuya Kobi-ro, Ryuichi Sugimoto, Kazuhiko Saigo, and Nagatoshi Nishiwaki

第 43 回複素環化学討論会, 10 月, **2013**, 岐阜.

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